FORMULATION AND EVALUATION OF BILAYER TABLET CONTAING PSEUDOEPHEDRINE HCL SR AND LORATADINE IR

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In

Pharmaceutics

by

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OCTOBER 2011.

CERTIFICATE

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ABBREVATIONS

gm	- Gram
ml	- Milliliters
mm	- Millimeters
cm	- Centimeters
BD	- Bulk Density
TD	- Tapped Density
CI	- Carr's Index
HR	- Hausner's Ratio
IR	- Immediate release
SR	-sustained release
^{o}C	- Centigrade
%RH	- Percentage Relative humidity
RPM	- Revolutions Per minute
HPMC	-Hydroxy Propyl Methyl Cellulose
SLS	-Sodium Lauryl sulfate
PVP	-Polyvinyl Pyrrolidone
API	-active pharmaceutical ingredient
HPLC	-High performance liquid chromatography

1. Introduction

The oral route of drug administration is the most important method of administering drug for systemic effect. More than 90% of the drugs used to produce systemic effect are administered by the oral route[1] Different types conventional dosage forms that are administered orally, such as solution, suspension, emulsion, tablets and capsules etc release the API into the absorption pool immediately. Upon administration of the dosage form the therapeutic plasma concentration is reached very quickly but does not maintain the drug level in the blood for an extended period of time. They have a very short duration of action. The short duration of action is due to inability of conventional dosage form to control temporal delivery. A drug blood level vs. time profile for a conventional dosage form administered orally is shown in the figure below.

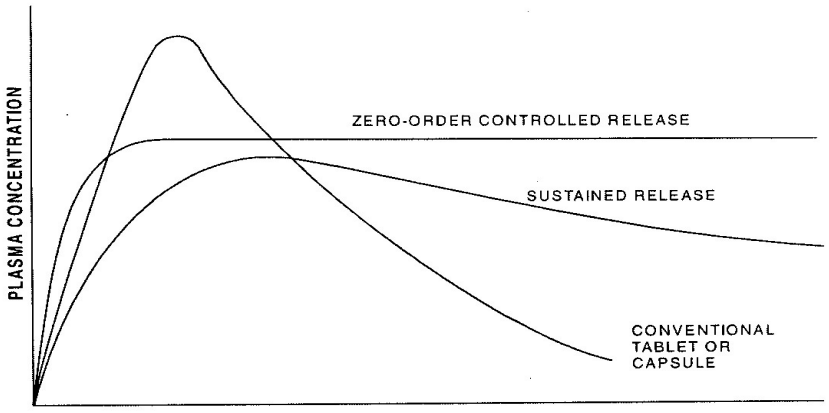


Figure no. 1 Plasma drug concentration profiles for conventional tablet or capsule formulation, a sustained release formulation and a zero order controlled release formulation.

To achieve and maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and thus results in a fluctuating drug level in plasma which is shown in the figure below.

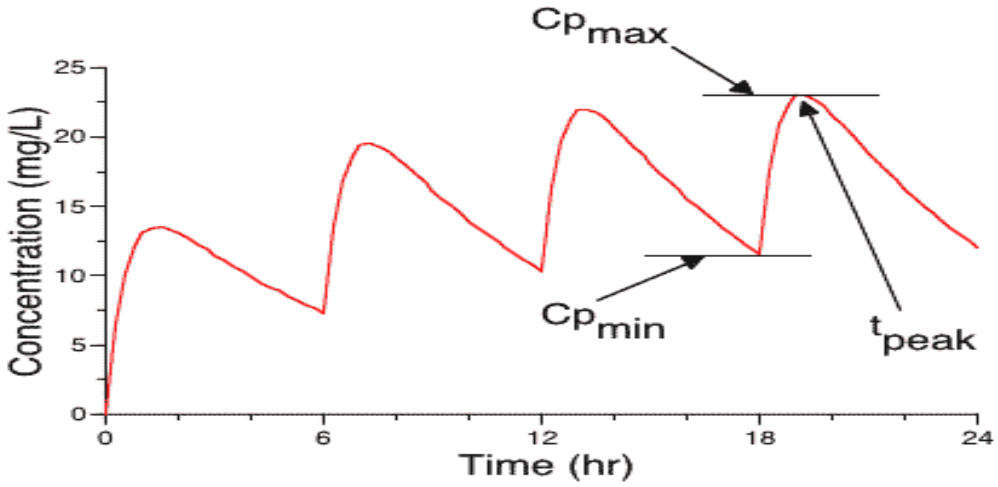


Figure no. 1 Plot of Cp versus time for multiple oral doses showing Cpmax and Cpmin

An ideal controlled drug delivery[2] system delivers the drug at a predetermined rate, locally or systemically for a specified period of time. Controlled drug delivery system not always release the drug by zero order kinetics .It may release by first order or any other kinetic model.

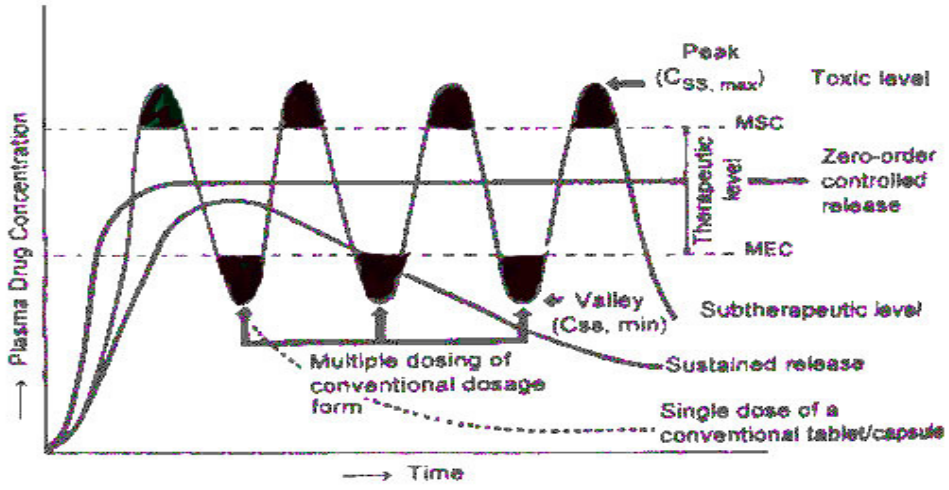


Figure no. 3 A hypothetical plasma concentration - time profile from conventional multiple dosing and single dose of sustained and controlled delivery formulations

In this case the level of the drug in the blood and the time required to reach that level depend upon the dose and the dosing interval. The potential problems associated with multiple dose therapy are :

1. If the interval is not appropriate, larger peaks and valley may results which may leads to adverse or toxic effects.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, which is important for certain diseases.
3. Poor patient compliance is observed as multiple daily doses are required.

So, these are the factors which lead to the investigation of sustained release drug delivery system.

2.1.1 Layered tablets

Layered tablets are composed of two or three layers of granulation compressed together. These are usually consisting of two and sometimes three layers. They have appearance of sandwich because the edges of each layer are exposed.

Fixed dose combinations with two or more ingredients can be formulated together in spite of actives having different physicochemical characteristics.

- Active-Active incompatibility.
- Actives may be thermal sensitive.
- Actives may be moisture sensitive.

2.1.2 Classification of layered tablets

A Layered tablets are classified as 3 types according to number of active ingredients

- Trilayered tablets having three different active ingredients.
- Bilayered tablets having two different active ingredients.
- Bilayered tablets having single active ingredients.

B Layered tablets are classified as the formulation type they are

- Bilayer tablets contain one immediate release and other sustained release.

- 2 Bilayer tablets contain both immediate release.
- Bilayer tablets of contain sustained and other inert layer as supporting.
- Bilayer tablets of one sustained release and other inert layer as protective.

2.1.3 Disadvantages of multilayer tablets

- Labour cost is high.
- Producion reduces to less than half.
- Proper weight adjustment of each layer is difficult during running of batch.
- Chances of lack of proper bonding of layers.
- Layer separation during storage.

2.1.4 Bi-Layer tablet

Bilayer tablet is defined as tablet consisting of two discrete zones consisting of same or different API intended for therapeutic action. A bilayer tablets consist of two layers. Bilayer tablets allows for designing and modulating the dissolution and release characteristics.

- Immediate release layer- Contains loading dose or I stdrug
- Sustained release layer- Contains maintenance dose or IInd drug

Immediate release layer of the dosage form contains the loading dose that delivers the entirety of its drug content at once after administration for the purpose of providing a rapid rise of drug concentration in the blood stream.

Sustained release layer of the dosage form contains the maintenance dose that gradually releases its drug content over a given period of time after administration for the purpose of providing a constant concentration of drug in lo the blood stream.

With two or more ingredients can be formulated together in spite of actives having different physico–chemical characteristics.

- Active -Active incompatibility
- Actives may be thermal or moisture sensitive.

- Bilayer tablets allows for designing and modulating the dissolution and release characteristics.

2.1.5 Bi-Layer Tablets are ideal for:

- Single agent pharmaceutical products.
- Combination therapy agent tablets with both agents in the same layer.
- Creation of new interrmediate dose.
- Titration and fine dose adjustments.

2.1.6 Advantages of bilayer tablets

Bilayer tablet have all advantages of combination drug delivery as well as additional advantages.

- Two or more drugs having different having different pharmacological action can be given in single dose
- Two or more drugs having different mechanism of action have been given in single dose
- Increase in patient compliance
- Decrease resistance of drug especially in case of antibiotics
- Cost effective
- Synergistic effect of two drugs
- Two incompatible drugs can be given.
- One drug is immediate release other is sustained release can be given.
- One is moisture sensitive other is not moisture sensitive can be given in bilayer tablets.
- One is enteric coated granules other drug is not enteric coated.
- Attractive appearance for marketing purpose.
- Different color layers for easy identification for a patient.
- One layer is water impermeable other layer for drug release such as mucoadhesion.

- Drug release of one which affects the release of other drug can be given as bilayer tablets.

2.1.7 Potential rationale for formulation development

- Patient compliance
- Immediate release of loratadine produces antihistamine effect without sedation.
- Minimum physical and chemical interaction
- Sustained effect of pseudoephedrine produce nasal decongestants effect for prolong period.
- Multiple medication management
- Economical than producing separate products for each active agent.

2.2 Sustained release drug delivery system[3,4,]

The term 'sustained release' is known to have existed in the medical and pharmaceutical literature for many decades. The term sustained release indicates an initially release of drug sufficient to provide a therapeutic dose soon after administration and gradual release over extended period.

The objective of sustained release of drug, in general way is to modify the normal behavior of drug molecule in a physiological environment. It can lead to the following.

1) Sustaining drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects.
2) Localization of drug action by spatial placement of controlled release system usually rate controlled adjacent to the or in the diseased tissue or organ.
3) Targeting drug action by using carriers or chemical derivatives to deliver drug to particular target cell type.

2.2.1 Advantages of sustained Release Dosage Forms[5]:

All sustained release products share the common goal of improving drug therapy over that achieved with their non-sustained counterparts. This improvement in drug therapy is represented by several potential advantages which are given below:

1. Better utilization of drug.
2. Reduced dose frequency
3. Improvement of patient compliance
4. Usage of less total drug
5. Reduction in local or systemic side effects
6. Minimization of drug accumulation (with chronic dosage)
7. More consistent and prolonged therapeutic effect.
8. Improvement in treatment efficiency
9. Improvement in speed of control of medical conditions
10. Reduction in drug blood level fluctuation
11. Improvement in bioavailability for some drugs

Generally, oral controlled release dosage forms should not be developed unless the recommended dosage interval for the controlled release dosage form is longer than that for immediate release dosage form or unless significant clinical advantages for the controlled release dosage form can be justified like the decreased side effects compared to the immediate release or conventional dosage form.

2.3 Matrix Devices:

A matrix device as the name implies, consists of a drug dispersed homogeneously throughout a rate-controlling medium. These include dissolution controlled release systems, diffusion controlled release systems and the combination of dissolution and diffusion controlled release systems. Release characteristics from matrix systems depend on the nature of the polymers, the additives, the drug and the geometry of the systems.

2.3.1 Reasons for restoring to matrix embedding:

Matrix systems offer several advantages such as controlling the dissolution rate of drugs having high aqueous solubility. They are easy to make and can be made to release high molecular weight compounds . As the drug is dispersed in the matrix system, accidental leakage of the total

drug component is less likely to occur and controlling the release kinetics of these devices is easier than for other systems, i.e. coated systems. Other advantages [11] include:

- Excipients used in these systems are generally cheap and are usually regarded as safe.
- Capable of sustaining high drug loading.
- Easy to manufacture by using commonly available equipment, by direct compression, wet granulation or by roll compaction.
- Possible to obtain different types of release profile: Zero order, first order, bimodal etc.

2.3.2 Matrix embedding techniques

These systems can be considered as two groups:

i) That with drug particles dispersed in soluble matrix, with drug being available as the matrix dissolves or swells and dissolves**.(Hydrophilic colloid matrices)**

ii) Those with drug particles dispersed in an insoluble matrix, with drug being available as a solvent enters the matrix and dissolves the particles **(lipid matrices and insoluble polymer matrices).**

Release of drugs dispersed in a soluble matrix relies on slow dissolution of the matrix to provide controlled release. In the case of drugs incorporated into an insoluble matrix, release follows penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores. The drug release from lipid matrix systems depends on an aqueous medium dissolving the channeling agents, which leaches out of the compact so forming porous matrix of tortuous capillaries.

The active agent dissolves in the aqueous medium and through the water filled capillaries diffuses out of the matrices.

(a) Hydrophilic colloid matrix system

This delivery system is also called swellable-soluble matrices. In general they comprise a compressed mixture of drug and water swellable hydrophilic polymer. On contact with water the hydrophilic colloid component swell to form a hydrated matrix layer. This then control the further diffusion of water into the matrix. Diffusion of the drug through the hydrated matrix layer

controls its rate of release. The outer hydrated matrix layer will erode as it becomes more dilute; the rate of erosion depends on the nature of the colloid.

Hydrophilic colloid gel can be regarded as a network of polymer fibrils that interlink in some way. There is also a continuous phase in the interstices between the fibrils through which the drug diffuses. These interstices connect together and are analogous to the tortuous capillaries seen in wax matrix. The tortuosity of the diffusion path and the 'microviscosity' and interactions within the interstitial continuum govern the diffusion of the drug through the hydrated gel layer, and hence the release of the drug.

Components of a hydrophilic matrix delivery system

- Active drug
- Hydrophilic colloid(s)
- Solubilizer / pH modifier
- Compression aid
- Lubricant
- Glidant

Matrix forming agents for hydrophilic matrices

Hydrophilic colloids which, on contact with water, form a hydrated gel that remains 'sufficiently intact' during passage through the GIT,are suitable matrix forming agent for hydrophilic matrices.

Examples of hydrophilic colloids include:

- Hydroxy propyl methyl cellulose (High viscosity grades
- Hydroxy ethyl cellulose and Hydroxy propyl cellulose
- Sodium carboxymethyl cellulose
- Alginates
- Xanthan gum
- Polyethylene oxide
- Carbopol

(b) Lipid matrix system

The lipid matrix systems are prepared from blends of powdered components. The active compound is contained in a hydrophobic matrix that remains intact during the drug release. Release depends on an aqueous medium dissolving the channeling agent, which leaches out of the compact so forming a porous matrix of tortuous capillaries. The active agent dissolves in the aqueous medium and, by way of the water-filled capillaries, diffuses out of the matrix.

A typical lipid matrix system consists of:

- Active drug
- Wax matrix former
- Channeling agent
- Solubilizer and ph modifier
- Antiadherant/Glidant
- Lubricant

(c) Insoluble polymer matrix system

An insoluble inert matrix system is one in which a drug is embedded in an inert polymer which is not soluble in the gastrointestinal fluid. Drug release from inert matrices has been compared to the leaching from a sponge.

The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles. The release rate of drug from an inert matrix can be modified by changes in the porosity and tortuosity of the matrix, i.e. its pore structure. The addition of pore forming hydrophilic salts or solute will have a major influence, as can the manipulation of processing variables. Compression force controls the porosity of the matrix, which in turn control drug release. Generally a more rigid and less porous matrix will release drug more slowly than a less consolidated matrix.

Methods:

The following methods may be used to disperse the drug in the matrix material.

i) Solvent evaporation techniques, in which a solution of matrix material is prepared in a suitable solvent, the drug is either dissolved or dispersed in it and then the solvent is removed by evaporation.

ii) Fusion technique, in which the drug is blended into the molten matrix material at temperatures slightly above the melting point of the drug and then the blend is either spray congealed or solidified and flaked or poured on a cold rotating drum to form sheets, which are then milled and screened to form granules. By this technique a more uniform dispersion can be prepared.

iii) Direct compression technique, in which dry blends of drug and matrix material are prepared, slugged and granulated.

2.3.3 Factors affecting release of drug from matrix

The following factors affect the release of drug from matrix systems.

- Viscosity of polymer
- Mixture of polymer
- Ratio of polymer to drug
- Particle size of drug
- Tablet thickness
- Compression pressure
- Added diluents
- Microenvironment pH of matrix
- Tablet surface area
- Entrapped air in tablet
- Drug solubility

2.3.4 Disadvantages of Controlled Release Dosage Forms[6]:

1) Increased variability among dosage units.
2) Toxicity due to dose dumping.
3) Poor in vitro-in vivo correlation.
4) Reduced potential for dosage adjustment.
5) Possible reduction in systematic availability
6) Delayed onset of action, which is not suitable for disease where quick onset and sustained action is required. E.g. Pain and inflammation requires quick onset and sustained action by the NSA

1.	Water insoluble, inert materials	Polyethylene, Polyvinylchloride, Methylacrylate-methacrylate copolymer, Ethylcellulose.
2.	Hydrophobic materials, insoluble-erodable (waxes)	Sterylalcohol, Stericacid, Polyethylene glycol, Carnaubawax, Casterwax, Polyethylene glycol monosterate, Triglycerides.
3.	Hydrophilic materials a) synthetic gums	Hydroxypropylmethylcellulose,Sodium carboxy methylcellulose (400 cps, 4000 cps), Hydroxy ethyl cellulose.
	b) Natural gums	Guar gum, Chitosan, Gum acacia, Tamarind seed polyose, Locustbeangum, Sod. Alginate, Karaya gum, Pectins, Xanthan gum.

Table No.1 Classification of retardant materials used in matrix tablets

2. Literature review

2.1 Littérature survey on bilayer tablet

Patra C.N. *et al*[7] developed a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. *In vitro* dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *In vitro* dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release. FTIR studies revealed that there was no interaction between the drug and polymers used in the study. Statistical analysis (ANOVA) showed no significant difference in the cumulative amount of drug release after 15 min, but significant difference ($p < 0.05$) in the amount of drug released after 12 hrs from optimized formulations was observed.

Chinam niranjan patra *et al* developed a Bilayered tablet of propanolol hydrochloride for the fast release layer and water immiscible polymers such as ethyl cellulose, Eudragit RLPO and Eudragit RSPO for the sustaining release layer the formulation gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 hours from the sustaining layer of matrix embedded tablets. The Both layers were prepared by wet granulation process.

Shiyani *et al*[8] prepared bi-layer tablet of Metoclopramide Hydrochloride (MTH) and Ibuprofen (IB) for the effective treatment of migraine. MTH and IB were formulated as immediate and sustained release layer respectively. MTH was formulated as immediate release layer MTH was formulated as immediate release layer by using various disintegrants like Ac-Di-Sol,Polyplasdone XL,Explotab, Agar and Gellan Gumand IB was formulated as sustained release layer using hydrophilic poymer HPMC K4M.

Vishnu M *et al*[9] The purpose of this research was to study mucoadhesive bilayer buccal tablets of propranolol hydrochloride using the bioadhesive polymers sodium alginate (Na-alginate) and Carbopol 934P (CP) along with ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface ph,mucoadhesive strength, swelling index, in vitro drug release, ex vivo drug permeation, ex vivo mucoadhesion, and in vivo pharmacodynamics in rabbits. Tablets containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of in vitro drug release without disintegration in 12 hours.

The swelling index was proportional to Na-alginate content and inversely proportional to CP content. The surface ph of all tablets was found to be satisfactory (7.0 ± 1.5), close to neutral pH; hence, buccal cavity irritation should not occur with these tablets. The mechanism of drug release was found to be non-Fickian diffusion and followed zero-order kinetics. The formulation F4 was optimized based on good bioadhesive strength (28.9 ± 0.99 g) and sustained in vitro drug permeation (68.65% ± 3.69% for 12 hours).

Rajashree Masareddy *et al* [10] developed floating matrix tablet of Riboflavin single and bilayer tablets were prepared by direct compression technique using polymers hydroxypropyl methyl cellulose, carbopol 971 P and other standard excipients. Carbopol containing tablets were retained in stomach by mucoadhesive mechanism and HPMC containing tablets were retained in stomach by non-mucoadhesive (floating) mechanism.

Remaya P.N. *et al*[11] developed the Bilayer tablets of Ibuprofen and Methocarbamol using Povidone K-30 as binder wet granulation process was used for the formulation of two layers and the tablet was film coated. This formulation is developed to separate the incompatible drug substances methocarbomol layer blend is initially pre-compressed with low hardness and Ibuprofen layer blend compressed over it.

Krishnaiah Y.S.R. *et al* (2002)[12] formulated three-layer matrix tablets of Metoprolol Tartrate by compressing on both sides of guar gum matrix tablet granules of Metoprolol Tartrate with either 50 or 75 mg of guar gum granules as release retardant layers. The amount of Metoprolol Tartrate

released from the three layer matrix tablets at different time intervals was estimated by using a HPLC method.

Narendra C. ***et al***[13] developed an optimized gastric floating drug delivery system (GFDDS) containing metoprolol tartrate (MT) as a model drug by the optimization technique. A 2^3 factorial design was employed in formulating the GFDDS with total polymer content-to-drug ratio (X_1), polymer-to-polymer ratio (X_2), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) (X_3) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, $T_{50\%}$, diffusion coefficient, and floating time. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that X_1 and X_2 significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was nonsignificant. Regression analysis and numerical optimization were performed to identify the best formulation. Fickian release transport was confirmed as the release mechanism from the optimized formulation. The predicted values agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development of GFDDS.

R. Nagaraju ***et al***[14] developed Bilayer sustained release tablets of salbutamol and Theophylline both layers were prepared by wet granulation technique. First layer (white layer) was the immediate release layer where the salbutamol was present. The Second layer (blue layer) was the sustained release layer where the salbutamol and Theophylline both were present. The release of theophylline should be completed within 8 hours, so that the Theophylline concentration in the body can be maintained for 12 hours. The release of the salbutamol should be completed with in 8 hours.

M A Naeem ***et al***[15] developed controlled release Bilayer tablets containing microencapsulated tramadol and Acetaminophen coacervation via temperature change was the encapsulation method used for the preparation of the microparticles with ethyl cellulose of medium viscosity as the polymer for extending drug release. The microparticles of two drugs were prepared separately and then compressed into bilayer tablets. Prolonged release upto 12 hours was

achieved thus making it feasible to attain educed frequency of administration of the drug combination.

united States Patent:7,157,100 to **Doshi *et al*.** describes a novel controlled release multilayer composition that is capable of delivering a first active agent from one layer immediately followed by continuous controlled delivery of second active agent from matrix forming layer while the dosage form floats and is retained in the fluid of the environment. The floating bilayer system comprises of immediate release layer containing one active agent and a disintegrating agent whereas second floating matrix forming layer comprises a gas generating component, a gelling agent, and a second active agent. This formulation is more particularly used to control release of fluoroquinolone compositions, which maintain a therapeutically effective blood concentration of fluoroquinolone for duration with once a day administration

European Patent no WO2006070406 discloses the preparation of a bilayer tablet of oxacarbazepine containing one immediate release layer of drug and a sustained release layer. This bilayer tablet maintains a therapeutically effective blood concentration of oxacarbazepine with once a day administration.

United States Patent 5407687 to **Mark D. Coffin** **Alan F. Parr** discloses the formulation of a bi-layer tablet having one layer formulated for the immediate release (IR) of ranitidine and a second layer formulated for sustained release (SR) of ranitidine with the ratio of ranitidine in the IR layer to that in the SR in the range of from about 30:70 to about 60:40. The IR layer comprises ranitidine, filler such as lactose, matrix agents such as microcrystalline cellulose and croscarmellose sodium, a lubricant such as magnesium stearate, and optionally other excipients and other active ingredients. The SR layer comprises ranitidine, a matrixing agent such as hydroypropylmethylcellulose, filler such as lactose, a lubricant such as magnesium stearate, and optionally other excipients and other

U.S. Patent No. 20060251721 to Atul D *et.al.* describes a Sustained release dosage forms for twice daily oral dosing to a human patient for providing relief from pain . The sustained release dosage form comprises an immediate release component and a sustained release component,

2.2 Literature survey on Sustained Release Formulations

Pal L. T. *et al*[16] designed an oral sustained release matix tablet of metformin HCl and to optimize the drug release profie using surface methology .Tablet were prepared by non aqueous wet granulation method using HPMC K15M. A central composite design for 2 factors at 3 level was employed to optimized drug release profile.

Reddy K. *et al*[17]developed an once-daily sustained-release matrix tablets of nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. According to the theoretical release profile calculation, a once daily sustained-release formulation should release 5.92 mg of nicorandil in 1 hour, like conventional tablets, and 3.21 mg per hour up to 24 hours. The results of dissolution studies indicated that formulation F-I (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 24 hours. In the further formulation development process, F-IX (drug-to-HPMC, 1:4; EC 4% w/v as granulating agent), the most successful formulation of the study, exhibited satisfactory drug

release in the initial hours, and the total release pattern was very close to the theoretical release profile. All the formulations (except F-IX) exhibited diffusion-dominated drug release. The mechanism of drug release from F-IX was diffusion coupled with erosion.

Satturwar P.M. ***et al***[18]. developed a controlled release of diclofenac sodium tablet using rosin derivative as hydrophobic matrix material. Matrix tablets were prepared by wet granulation method using R-1 as matrix forming material in different proportions and combinations. The matrix tablets were evaluated for thickness, hardness, friability, weight variation, drug content uniformity ans in vitro dissolution. The results suggest that the new rosin derivative (R-1) is useful in developing sustained release matrix tablets, with drug release being prolonged for upto 10 h.R-1 thus promises considerable utility in the development of oral sustained relapse drug delivery.

Patro S.S. ***et al*** [19] developed guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. Matrix tablets of diltiazem hydrochloride, using various viscosity grades of guar gum in 2 proportions, were prepared by wet granulation method and subjected to in vitro drug release studies. Diltiazem hydrochloride matrix tablets containing either 30% wt/wt lowviscosity (LM1), 40% wt/wt medium-viscosity (MM2), or 50% wt/wt high-viscosity (HM2) guar gum showed controlled release. The drug release from all guar gum matrix tablets followed first-order kinetics via Fickian-diffusion. Further, the results of in vitro drug release studies in simulated gastrointestinal and colonic fluids showed that HM2 tablets provided controlled release comparable with marketed sustained release diltiazem hydrochloride tablets (D-SR tablets). Guar gum matrix tablets HM2 showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40°C/RH 75% for 6 months. When subjected to in vivo pharmacokinetic evaluation in healthy volunteers, the HM2 tablets provided a slow and prolonged drug release when copared with D-SR tablets. Based on the results of in vitro and in vivo studies it was concluded that that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride

3. Objective and aim:

Today, the scenario of pharmaceutical drug delivery is changing from conventional dosage form to new drug delivery system with main objective of patient compliance. There are certain conditions like pain, inflammation, arthritis, ankolysing spondylitis, seasonal allergic rhinitis (SAR), etc where it is desirable to extend the dosing interval of many pharmaceuticals while maintaining the initial plasma concentrations achievable with conventional tablets. This would provide immediate and extended therapeutic effect and reduce the number of doses necessary, thereby making therapy more convenient.

Combination formulation of two or more active ingredients, are being designed to combat many clinical conditions like seasonal allergic rhinitis, cardiovascular diseases. SAR is associated with sneezing, lachrymal and nasal secretion and nasal congestion.

Thus for management of these conditions patient with this disease have to take multiple medication for long periods of time.

This can be overcome by formulating a tablet containing two layers, one containing the immediate release layer and one containing the sustained release layer. A bilayer tablet can achieve the initial plasma concentrations achievable with conventional tablets of one drug and maintain for long time as sustained release tablets of other drug.

Hence the main aim of the present study is to formulate a bilayer tablet loratadine containing an immediate release layer and a pseudoephedrine HCl as sustained release layer .The main objective of the present study is to formulate an immediate release layer which releases the loratadine quickly and produce antihistamine effect which suppress histamine induce effect sneezing, lachrymal and nasal secretion without sedation and sustained layer of pseudoephedrine which produce nasal decongestion effect by using polymers in matrix such that the drug release can be prolonged for 12 hours.

4. Plan of work

1. Literature survey on the drug, polymers, technology and other excipients.
2. Preformulation studies
    a. Physicochemical characterization of the drug
    b. Solubility studies of drug in different medium
    c. Interaction studies by FTIR
    d. Selection of suitable method for analysis of drug or development of standard graph for the drug.
3. Formulation of bilayer tablets of pseudoephedrine HCl & loratidine
4. Physical evaluation of the dosage forms
5. In-vitro drug release studies.
6. Kinetic of drug release studies
7. Stability studies

5.DRUGS PROFILE

5.1 Pseudoephedrine20,21,22 HCL

IUPAC Name	(1*S*,2*S*)-2-methylamino-1-phenylpropan-1-olHydrochloride
Empirical formula	$C_{10}H_{15}NO,Cl$
CAS	345-78-8
Molecular Weight	201.7

Table No.2: General description

Structural formula:

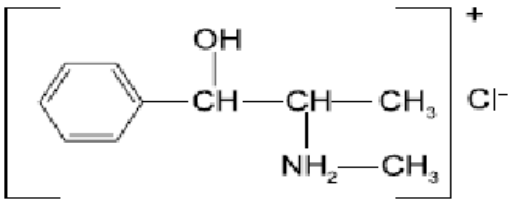


Figure No. 4

Color and Appearance	white or almost white, crystalline powder
Melting range	118° -118.7°C
Solubility	Freely Soluble H_2O, Freely soluble alcohol and ether
Polymorphism	Exhibits no polymorphism
Optical rotation	-61°+62.5
$_P$ka	9.9
pH	4.5 – 6(water)

Table No.3: Physical properties

Absorption	Rapid form GIT
Onset of action	Decongestant: Oral: 15-30 minutes
Metabolism:	Partially hepatic
Half-life elimination	9-16 hours
Excretion	Urine (70% to 90% as unchanged drug, 1% to 6% as active norpseudoephedrine)
Duration	Immediate release tablet: 4-6 hours; Extended release:12 hours

Table No.4:Pharmacodynamics/Kinetics

Dosage:

Oral: General dosing guidelines:

Children:

<2 years: 4 mg/kg/day in divided doses every 6 hours

2-5 years: 15 mg every 4-6 hours; maximum: 60 mg/24 hours

6-12 years: 30 mg every 4-6 hours; maximum: 120 mg/24 hours

Adults: 30-60 mg every 4-6 hours, sustained release: 120 mg every 12 hours; maximum: 240 mg/24 hours.

Mode of action:

Pseudoephedrine is a sympathomimetic amine—that is, its principal mechanism of action relies on its indirect action on the adrenergic receptor system. While it may have weak agonist activity at α- and β-adrenergic receptors, the principal mechanism is to cause the release of endogenous norepinephrine (noradrenaline) from storage vesicles in presynaptic neurons. The displaced noradrenaline is released into the neuronal synapse where it is free to activate the aforementioned postsynaptic adrenergic receptors.

These adrenergic receptors are located on the muscles lining the walls of blood vessels. When activated by pseudoephedrine, the muscles contract, causing the blood vessels to constrict (vasoconstriction). These constricted blood vessels now allow less fluid to leave the blood vessels and enter the nose, throat and sinus linings, which results in decreased inflammation of nasal membranes as well as decreased mucus production.

Vasoconstriction in the nasal mucosa shrinks swollen nasal mucous membranes, reduces tissue hyperemia, edema, and nasal congestion. Other beneficial effects may include increasing the drainage of sinus secretions, and opening of obstructed Eustachian tubes..

Indications

Pseudoephedrine is indicated for the treatment of:

- nasal congestion

- sinus congestion
- Eustachian tube congestion.

Adverse effects

Common adverse drug reactions (ADRs) associated with pseudoephedrine therapy include: CNS stimulation, sleeplessness, nervousness, excitability, dizziness and anxiety. Infrequent ADRs include: tachycardia and/or palpitations. Rarely, pseudoephedrine therapy may be associated with hallucinations, arrhythmias, hypertension, seizures and ischemic colitis; as well as severe skin reactions known as recurrent pseudo-scarlatina, systemic contact dermatitis, and nonpigmenting fixed drug eruption.Pseudoephedrine, particularly in high doses, may also cause episodes of paranoid psychosis. It has also been reported that pseudoephedrine, amongst other sympathomimetic agents, may be associated with the occurrence of stroke.

Precautions and contraindications:

It is recommended that pseudoephedrine not be used in patients with: diabetes mellitus, cardiovascular disease, hypertension, prostatic hypertrophy, hyperthyroidism, closed angle glaucoma and/or pregnancy. Contraindications for the use of pseudoephedrine include: concomitant or recent (previous fourteen days) monoamine oxidase inhibitor (MAOI) therapy, severe or uncontrolled hypertension, and/or severe coronary artery disease.

5.2 Loratadine[23,]

Molecular weight	382.9
CAS	79794-75-5
Empirical Formula	$C_{22}H_{23}ClN_2O_2$
IUPAC Name	Ethy4-(8-chloro-5,6-dihydro-11H benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-piperidinecarboxylate.

Table No.5 : General description Table

Structural formula:

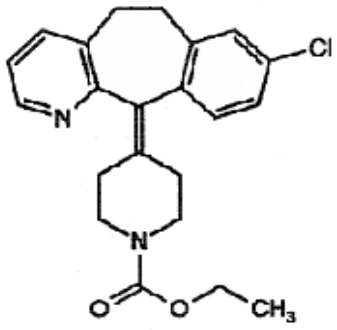


Figure No. 5

Color and Appearance	A white to off - white, fluffy powder
Melting range	118°C
Solubility	Insoluble in water, freely soluble acetone, alcohol, chloroform.
Polymorphism	Exhibits no polymorphism.
Optical rotation	No optical rataion
pKa value	2.5,4.0,6.7,10.1 (by aqueous acidic/basic potentiometer titration at 25°C)
Hygroscopic nature	slightly hygroscopic
Partition coefficient	10.2±0.5 in phosphate buffer(0.1M,pH-7)/ n-octanol system at room temp.

Table No.6: Physical properties

Onset of action	1-3 hours
Peak effect	8-12 hours
Duration	>24 hours
Absorption	Rapid
Metabolism	Extensively hepatic via CYP2D6 and 3A4 to active metabolite
Half-life elimination	12-15 hours
Excretion	Urine (40%) and feces (40%) as metabolites
BCS	class II
Binding	98%bound to Plasma Protein
Metabolite	Desloratadine(12-24 hours)

Table No.7:**Pharmacokinetics / Pharmacodynamics**

Parameters	LOR
C_{max}	17±14/µg-L^{-1}
T_{max}	1.2±0.6 h
$T_{1/2}$	6±4 h

Table No.8 Pharmacokinetic parameters of loratadine after a single oral dose of 20 mg

Indications

Loratadine is indicated for the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticaria (hives), and other skin allergies.For allergic rhinitis (hay fever), loratadine is effective for both nasal and eye symptoms: sneezing, runny nose, itchy or burning eyes.

Mechanism of action:

Loratadine is a tricyclic antihistamine, which selectively antagonizes peripheral histamine H_1-receptors.Loratadine has a long-lasting effect and does not normally cause drowsiness because it does not readily enter the central nervous system.

Side-effects

Non-sedating antihistamine as a non-sedating antihistamine, loratadine causes less sedation and psychomotor impairment than the older antihistamines because it penetrates the blood brain barrier only to slight extent.Although drowsiness is rare, patients should nevertheless be advised that it can occur and may affect performance of skilled tasks (e.g. driving); excess alcohol should be avoided.

Most common side-effects

Drowsiness, headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastrointestinal disturbances are the most common side effects.

Dosage

Oral: Seasonal allergic rhinitis, chronic idiopathic urticaria:

Children 2-5 years: 5 mg once daily

Children :6 years and Adults: 10 mg once daily

Cautions and contraindications

Loratadine should be used with caution in hepatic disease and dose reduction may be necessary in renal impairment. Caution may be required in epilepsy. Children and the elderly are more susceptible to side-effects. Loratadine is a category L-2 (classified by the American Academy of Pediatrics as a drug "Usually Compatible with Breast-feeding and category B in pregnancy.

LACTOSE MONOHYDRATE[24]

Applications in pharmaceutical formulation: Lactose is widely used as a filler or diluent in tablets and
capsules, and to a more limited extent in lyophilized products
and infant formulas.(1–13) Lactose is also used as a diluent in drypowder inhalation..

Incompatabilities: Lactose is also incompatible with amino acids, aminophylline,(
19) amfetamines,(20) and lisinopril.

Safty: Lactose is widely used in pharmaceutical formulations as a filler
and filler-binder in oral capsule and tablet formulations. It may
also be used in intravenous injections.

Sodium lauryl sulfate[25]

synonyms

Dodecyl alcohol hydrogen sulfate, sodium salt, dodecyl sodiumsulfate, dodecylsulfate sodium salt, lauryl sodium sulfate, lauryl sulfate, sodium salt, monododecyl sodium sulfate, sodium dodecyl sulfate, sodium laurilsulfate, sodium monododecyl sulfate, sodium monolauryl sulfate, SDS, SLS, sulfuric acid monododecyl ester, sodium salt, Texapon K12P.

Description

Sodium lauryl sulfate consists of white colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

Functional category

Anionic surfactant, detergent, emulsifying agent, skin penetrant, and wetting agent.

Applications in pharmaceutical formulation

1. Sodium lauryl sulfate is an anionic surfactant used in nonparenteral pharmaceutical formulations and cosmetics.
2. sodium lauryl sulfate is a detergent and wetting agent effective in both alkaline and acidic conditions.

Stability and storage conditions

Sodium lauryl sulfate is stable in normal storage conditions. Sodium lauryl sulfate in solutions, at pH 2.5 or below, undergoes hydrolysis to lauryl alcohol and sodium bisulfate. stored in a well closed container in a cool, dry place.

Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, results in loss of activity. Sodium lauryl sulfate is incompatible with salts of metal ions, such as aluminum, lead, tin or zinc, and precipitates with potassium salts. Solutions of sodium lauryl sulfate (pH 9.5–10.0) are corrosive to steel, copper, brass, bronze, and aluminum.

Safety

Sodium lauryl sulfate is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin.

Microcrystalline Cellulose[26]

Synonyms

Avicel, Cellets, Celex, cellulose gel, hellulosum, microcristallinum, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

Description

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder.

Functional category

Adsorbent, suspending agent, Tablet and capsule diluent,

Applications in pharmaceutical formulation

1. Microcrystalline cellulose is used as a binder, diluent in oral tablet and capsule formulations.
2. Microcrystalline cellulose also has lubricant and disintegrant properties

Stability and Storage Conditions

Microcrystalline cellulose is hygroscopic material. Stored in well closed container and protect from moisture.

Incompatibilities

Microcrystalline cellulose is incompatible with strong Oxidizing agent.

Safety

Microcrystalline cellulose is nontoxic and nonirritant material.

MAGNESIUM STEARATE[27].

Non-proprietary names - BP: Magnesium stearate, JP: Magnesium stearate, PhEur: Magnesii stearas.

Synonyms - Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name - Octadecanoic acid magnesium salt.

Empirical Formula and Molecular Weight - $C_{36}H_{70}MgO_4$ and 591.34.

Description - The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula - $[CH_3 (CH_2)_{16}COO]_2Mg$.

Functional Category - Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology - Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 and 5.0% w/w. It is also used in barrier creams. Description magnesium stearate is a very fine, light white, precipitated or milled,

impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Crystalline forms - high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate and an anhydrate.

Density (bulk): 0.159 gm/cm^3.

Density (tapped): 0.286 gm/cm^3.

Density (true): 1.092 gm/cm^3.

Flash point: 250°C.

Flow ability: poorly flowing, cohesive powder.

Melting range: 117–150°C (Commercial samples),

126–130C (High purity magnesium stearate).

Solubility - Practically insoluble in ethanol, ethano

TALC[28]

Synonyms : Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc;

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Category: Anticaking agent; glidant; tablet and capsule diluent; tablet

Aplications in pharmaceutical formulation: Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, see Table I,(1–3) although today it is less commonly used. However, it is widely used as a dissolution

retardant in the development of controlled-release profile

Incompatibilities:
Incompatible with quaternary ammonium compounds.

ISOPROPYL ALCOHOL[29].

Non-proprietary names - BP: Isopropyl alcohol, JP: Isopropanol, PhEur: Isopropyl alcohol, USP: Isopropyl alcohol.

Synonyms -Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl alcohol and rubbing alcohol.

Empirical Formula and Molecular Weight - C_3H_8O and 60.1.

Functional Category - Disinfectant and solvent.

Applications in Pharmaceutical Formulation or Technology -Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity; although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation,(2) where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Typical Properties - Antimicrobial activity Isopropyl alcohol is bactericidal; at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%). The bactericidal effect of aqueous solutions increases steadily as the concentration approaches 100% v/v. Isopropyl alcohol is ineffective against bacterial spores.
Autoignition temperature is 425°C. Boiling point 82.4°C. Dielectric constant D20 = 18.62.

Explosive limits 2.5–12.0% v/v in air. Flammability Flammable: Flash point 11.7°C (closed cup), 138°C (open cup). The water azeotrope has a flash point of 16°C.

Melting point - 88.5°C. Moisture content is 0.1–13% w/w for commercial grades (13% w/w corresponds to the water azeotrope). Solubility: Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water. Soluble in acetone and insoluble in salt**.**

6. POLYMERS PROFILE

6.1 HPMC[30]

1. Synonyms

Benecel MHPC; Cellulose, hydroxypropyl methyl ether; E464; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Pharmacoat.

2. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether [9004-65-3]

3. Empirical Formula Molecular Weight

The PhEur describes hydroxypropyl methylcellulose as a partly O-methylated and O-(2-hydroxypropylated) cellulose.

Hydroxypropyl methylcellulose defined in the USP specifies the substitution type by appending a four digit number to the nonproprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CHOHCH3), calculated on a dried basis.

1. **Structural Formula**

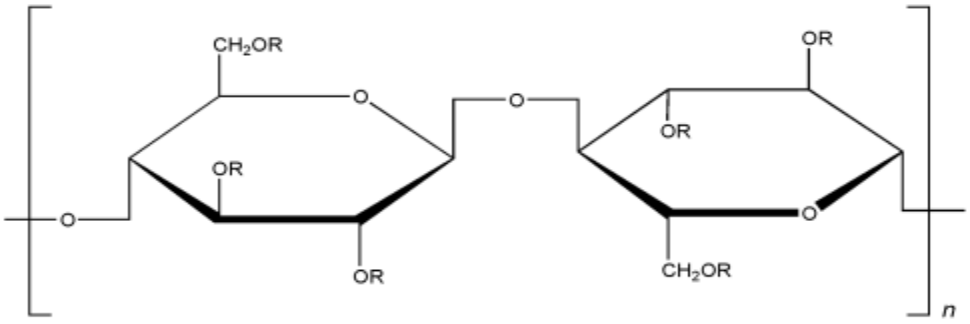


Figure No. 6

Where R is H, CH3, or [CH3 CH(OH)CH2].

5. Functional Category

Coating agent, film-former, rate-controlling, polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

6. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.In oral products; hydroxypropyl methylcellulose is primarily used as a tablet binder, in film-coating and as an extended-release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80% w/w in tablets and capsules.

In addition, hydroxypropyl methylcellulose is used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

7. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder..

8. Typical Properties

Acidity/alkalinity:

pH = 5.5-8.0 for a 1% w/w aqueous solution.

Ash: 1.5-3.0%, depending upon the grade.

Autoignition temperature: 360°C

Density (bulk): 0.341 g/cm3

Density (tapped): 0.557 g/cm3

Density (true): 1.326 g/cm3

Melting point: Browns at 190-200°C; chars at 225-230°C. Glass transition temperature is 170-180°C.

Specific gravity: 1.26

9. Stability and Storage Conditions

Hydroxypropyl methylcellulose powder is a stable material although it is hygroscopic after drying.

Hydroxypropyl methylcellulose powder should be stored in a well-closed container, in a cool, dry, place.

10. Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts or ionic organics to form insoluble precipitates.

11. Safety

Hydroxypropyl methylcellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.

12. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl methylcellulose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions. Hydroxypropyl methylcellulose is combustible.

6.2 Ethylcellulose (Ethocel med 50)[31]

1. Synonyms :*Aquacoat ECD*; ***Aqualon***; **E462**; ***Ethocel***; ***Surelease***.

2. Chemical Name and CAS Registry: NumberCellulose ethyl ether [9004-57-3]

3. **Empirical Formula and Molecular Weight:** Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

4. Structural Formula:

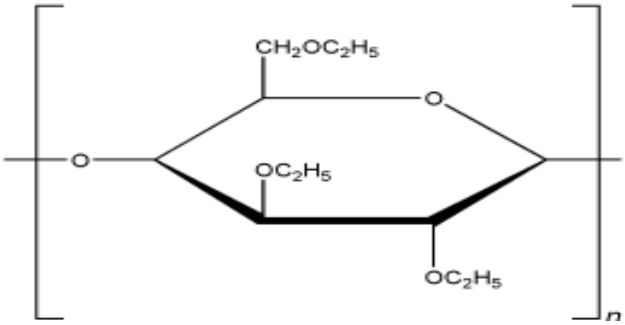


Figure No. 7

2. Functional Category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

TableNo.9: Applications of HPMC in pharmaceutical formulation or technology

In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

6. Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder

7. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range.

8. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Grade	**Solution viscosity (mPa s)** **Mean particle size (μm)**	
Ethocel Std 45P Premium	41.0–49.0	—
N-50	40.0–52.0	—
N-100	80.0–105.0	—
Ethocel Std 100FP Premium	90.0–110.0	30.0–60.0

Grade	Solution viscosity (mPa s) Mean particle size (µm)	
Ethocel Std 45P Premium	41.0–49.0	—
Ethocel Std 100P Premium	90.0–110.0	465.0
Ethocel med 50	55.0-60	262

Table No. 10: **Ethylcellulose grades,, viscosity, and particle size**

7.1 Materials:

S. No.	Excipient	Category
1	Loratadine	API
2	Corn Starch	Diluent
3	LactoseMonohydrate	Diluent and binder
4	Microcrystalline Cellulose (Avicel PH 102)	Diluent
5	Aerosil	Binder
6	Sodium lauryl sulfate	Wetting agent
7	Magnesium Stearate	Lubricant
8	Sunset yellow colour	Color
9	Talc	Glident

Table No.11: Materials for immediate release layer (Loratadine)

S. No.	Excipient	Category
1	Pseudoephedrine HCl	API
2	HPMC K100M	Hydrophilic polymer
3	Ethyl cellulose	Polymer ,binder
4	Dicalcium phosphate dihydrate	Diluent
5	Colloidal Silicon Dioxide (Aerosil-200)	Glidant
6	Polyvinylpyrollidone [PVP K30])	Binder
7	Talc	Glidant
8	Isopropyl alcohol IP	Vehicle
9	Magnesium stearate	Lubricant

Table No. 12: Materials for sustained release (Pseudoephedrine HCl layer)

7.2 Equipments used in formulation development

S.No	Equipment	Manufacturer
1.	Electronic Weighing Balance	Electrolab
2.	Rapid mixer granulator(2.0L)	Bacto chem. Pvt. Ltd.
3.	Rapid dryer	Retsch
4.	Multi mill	SSPM Pvt. Ltd.
5.	Compression machine	Karanavathi
6.	Induction cap sealer	Electronic devices
7.	Hardness tester	Schleniger pharmaton
8.	Friabilator	Electrolab
9.	Disintegration test apparatus	Electrolab
10.	Dissolution apparatus	Electrolab
11.	Halogen moisture analyser	Mettler Toledo
12.	Bulk density apparatus	Electrolab
13.	Sieve Shaker	Retsch
14.	Mechanical sifter	SSPM Pvt. Ltd.
15.	HPLC	Waters

Table no: 13 Equipments used in formulation development

8. Preformulation Study[32]:

Preformulation testing is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipient. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailability dosage forms that can be mass produced.

Following the identification of a new chemical entity that is suitable for development, the formulator will be called upon to produce dosage form. Initially this may involve production of Injectable form suitable for early efficiency and toxicity testing and subsequently there with be a need to develop the final dosage form which generally with not be Injectable. The challenge for the formulator is to develop the initial and final dosage form to the highest quality in shortest time. This process is best achieved when certain physicochemical properties of the drug substance are investigated understood and effectively utilized; this is preformulation.

Need of preformulation studies

Scientific and regulatory justification of acquiring Preformulation data includes the following.

1) Establishment of drug specification intended for toxicological evaluation and clinical supply preparation.
2) Formulation of clinical supplies and establishment of their preliminary specification.
3) Providing scientific data to support dosage form development and evaluation of product efficacy, quality, stability and bioavailability.
4) Evaluation of the stability of early developed dosage forms.
5) Fulfillment of the requirement of the Chemistry Manufacturing Control section of the Investigational New Drug[23] (IND) and subsequent New Drug Application (NDA) or Abbreviated New Drug Application (AND).

8.1 Preformulation study can divided into two subclasses[33].

1) Active pharmaceutical ingredient (API) characterization:

Organoleptic evaluation

These are preliminary characteristics of any substance, which is useful in identification of specific material. Following physical properties of API were studied.

- Color
- Taste
- Odor

2) Compatibility study

The compatibility of drug and formulation components is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

8.2 Preformulation studies include investigation of

I. Bulk characterization

a. Crystallinity and polymorphism
b. Hygroscopicity
c. Fine particle characterization
d. Bulk density
e. Powder flow properties

II. Solubility analysis

a. Ionization constant – pKa

b. pH solubility profile

c. Common ion effect

d. Thermal effect

e. Solubilization

f. Partition coefficient

g. Dissolution

III. Stability analysis

- Solid state stability of drug alone
- Stability in presence of excipient (Compatibility studies)
- Solution phase stability (Stability in gastrointestinal fluid and granulating solvents)

IV. Photo stability studies

(1) Evaluation of physical properties of drug (Bulk characterization)

1. Angle of repose

Flowability[24] of mixture was determined by calculating angle of repose by fixed height method. A funnel with 10 mm diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose was calculated from the average radius using the following formula.

Angle of repose	Flow characteristics
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Table No.11: Flow Characteristics

$\theta = \tan^{-1} (h/r)$

Where,

θ = Angle of repose.

h = Height of the pile.

r = Average radius of the powder cone

API	Height(Cm)	Radius(Cm)	Angle of repose(θ)	Flow Characteristics
Pseusdoephedrine	2.9	4.0	35.94°	Passable
Loratadine	Very fine powder			Very poor

Table No. 14: Results of angle of repose (θ) and flow characteristics of API'S

2. Bulk density

Bulk densities of all types of mixture were determined by pouring gently 10 gm of sample through a glass funnel into a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated.

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample}}{\text{Volume accupied by the sample}}$$

API	Bulk Density (gm/ml)
Pseudoephedrine	0.601
Loratadine	0.199

Table No. 15: Results of bulk density of API'S

3. Tapped density

Tapped density was determined by using electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (50 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

$$\text{Tapped density [g/ml]} = \frac{\text{Weight of sample}}{\text{Volume accupied by the sample}}$$

API	Tapped Density (gm/ml)
Pseudoephedrine	0.683
Loratadine	0.293

Table No.16: Results of tapped density of API's

4. Compressibility (%):

It is also one of the sample methods to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide in given by the Carr's compressibility.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

API	Bulk Density	Tapped Density	Compressibility index (%)
Pseusdoephedrine	0.544	0.683	12.00
Loratadine	0.601	0.293	31.43

Table No. 17: Results of compressibility (%) of API's

Compressibility Index (%)	Flow Character
<10	Excellent
11–15	Good
16–20	Fair
21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very, very poor

Table No.18: Relationship of flow character with compressibility index (%)

5. Hausner ratio:

It provides an indication of the degree of densification which could result from vibration of feed hopper

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

<1.2 =Free Flowing

1.2-1.8 =Cohesive

API	Bulk Density	Tapped Density	Hausner ratio	Flow Characteristics
Pseusdoephedrine	0.544	0.683	1.136	Free flowing
Loratadine	0.601	0.293	1.472	Cohesive

Table No.19: Results of flow characteristics Hausner's ratio of API's

6. Sieve Analysis[34]

The main aim of analysis is to determine the different size of drug particles present. A series of standard sieves were stacked one over the above so that sieves with larger pore size (Less Sieve No) occupy top position followed by a series of decreasing pore size (Larger Sieve No) towards the bottom.

Procedure: The procedure involves the Electromagnetic Sieve shaking of the sample through the series of successively arranged sieves (sieve no. - 20,30,60,80,100 and receiver), and

weighing of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

50gram of both blend of pseudoephedrine HCl electromagnetic sieve shaking and weighing of the portion of the sample retained on each sieve and calculates percentage retained on each sieve.

Sieve No. Used	Pore Size in µm	% Retained	Cumulative % Retained
20	850	0	0
30	600	4.94	4.94
60	250	70.7	75.64
80	180	12.4	88.04
100	150	10.2	98.24
BASE	NA	1.76	100

Table No. 20: **Sieve analysis observation of pseudoephedrine HCl**

7. Loss on drying:

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions the test is carried on a well mixed sample of the substance. If the substance is the form of large crystals reduce the size by rapid crushing to a powder.

B.Method II:

0.5g of sample of pseudoephedrine & loratadine blend was accurately weighed and the powder was kept in a Mettler Toledo apparatus for 5 min. at 105ºC and the moisture content was calculated.

API	L.O.D.
Peudoephedrine	0.42%

Loratadine	0.37%

Table No.21: Loss on drying results of API's

(2) Solubility Analysis[35]:

1. Drug pKa & pH:

The amount of drug that exists in unionized form is a function of dissociation constant (pKa) of the drug it is customary to express the dissociation constants of both acidic and basic drugs by pKa values**.** Lower the pKa of an acidic drug stronger the acid i.e. greater the proportion of ionized form at a particular pH. The higher the pKa of basic drug, the stronger the base. Thus from the knowledge of pKa of the drug and ph at absorption site (or biological fluid).the relative amount of ionized and unionized drug in solution at a particular pH and the percent of drug ionized at this ph can be determined by Henderson-hasselbach equation

$$\text{For Weak acids: } pH = pKa + \log \frac{\text{ionized drug concentration}}{\text{unionized drug concentration}}$$

$$\textbf{\% Drug Ionized} = \frac{10^{pH-pKa}}{1+10^{pH-pKa}} \times 100$$

$$\text{For weak base: } pH = pKa + \log \frac{\text{unionized drug concentration}}{\text{ionized drug concentration}}$$

$$\textbf{\% Drug Ionized} = \frac{10^{pKa-pH}}{1+10^{pKa-pH}} \times 100$$

For weak Acids:

1. Very weak acids (pKa>8) such as phenytoin and several barbiturates are essentially unionized at all pH values and therefore their absorption is rapid and independent of GI pH

2. Acids in pKa range 2.5 to 7.5 are generally affected by changes in ph and therefore their absorption is pH dependent e.g. several NSAIDS like aspirin, ibuprofen are better absorbed from acidic condition of stomach

3. Stronger acids with (pKa<2.5) such as cromolyn sodium are ionized in the entire pH range of GIT and therefore remain poorly absorbed

For Weak base:

1. Very weak base (pKa<5) such as caffeine, theophylline, carboxylic acid derivatives are essentially unionized at all pH values and therefore their absorption is rapid and pH independent

2. Bases in the pKa range 5 to 11.0 are generally affected by change in pH and hence their absorption is pH-dependent. Such drug are better absorbed from the relatively alkaline conditions of the intestines where they are largely exist in unionized form

3. Stronger Bases with pKa> 11.0 like mecamylamine are ionized in the entire pH range of GIT0 and therefore poorly absorbed.

Effect of pH on the Absorption of pseudoephedrine Drug

pKa of pseudoephedrine Drug~9.9 therefore their absorption is rapid and independent of GI pH

Effect of pH on absorption of loratadine drug:

pKa of loratadine is~4.2(Moderately weak acid)

pH	% Drug Ionized	% Drug unionized	Absorption
1.0	0.31%	99.69%	Absorbed rapidly
3.2	66.61%	33.40%	Absorbed rapidly
4.2	83.378	17.73%	Absorption decreases

5.2	98.043	1.96%	Poor Absorption
7.5	99.990	0.11%	Very poor Absorption

Table No.22: Effect of pH on the absorption of loratadine

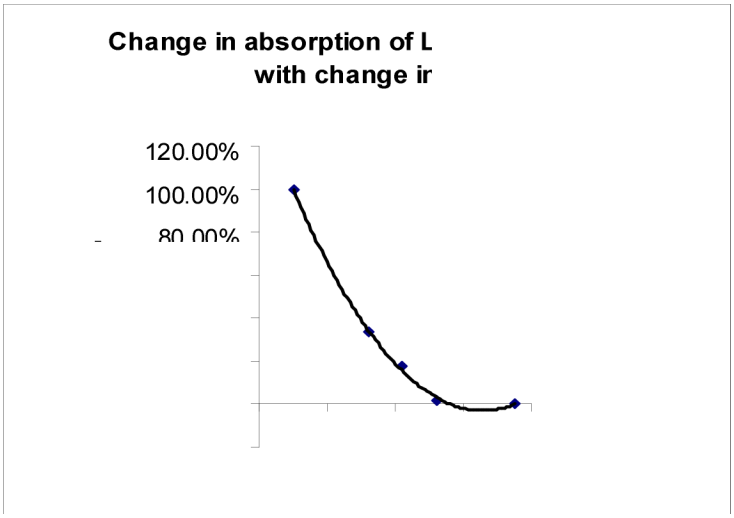


Figure No. 8

2. pH solubility profile

It is recommended that the pH-solubility profile of the test drug substance should be determined at 37 ±1 ^{0}C in aqueous media with a ph in the range of 1.0-7.5. According to the FDA Guidance, the number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. When the pKa value of drug is in the range of 3-5, the solubility should be determined at pH=pKa, pH=pKa+1, pH=pKa-1 and at pH = 1.0 and 7.5. Pseudoephedrine has a pKa of 9.9 and loratadine has a pKa of 4.4. Therefore, the solubility of pseudoephedrine and loratadine was determined in 0.1N HCl , D.M. water , 4.5 pH acetate buffer , 5.5 pH acetate buffer & 6.8 pH phosphate buffer . Experimental results showed that aspirin has

a pH dependent solubility. Solubility of aspirin increases when the pH of the medium increased from 1.0 to 7.5.

pH, pKa and solubility: Solubility is influenced by the degree of ionization of the substance. Total aqueous solubility of an ionizable substance can be expressed as:

$S_T = [HA] + [A^-]$ for a weak acid

$S_T = [B] + [BH^+]$ for a weak base

Or $S_T = S_{HA} + [A^-]$ for a weak acid

$S_T = S_T + [BH^+]$ for a weak base

Where ST is the total solubility and SHA and SB are the solubilities of the unionized weak acid or weak base.

For a non-ionizable substance, a non-electrolyte:

$S_T = SNE$

For a weak acid, the following equation can be derived:

$$S_T = S_{HA} + KaS_{HA} / [H_3O^+]$$

Which indicates that solubility of a weak acid increase with increasing ph (decreasing H3O+ concentration) so as ↑ pH then ↓HA, ↑A^-, and ↑ST?

Correlation with Henderson Hasselbach: Maximum aqueous solubility for weak acids is attained at pH-pKa » 2, where 99% is in the ionized (A-) form. Minimum solubility is at pH-pKa » -2 where 99% is in the unionized (HA) form. The logarithmic form can be used to predict the pH (pHp) below which the unionized weak acid would precipitate from solution:

$$pHp = pKa + \log S_T - S_{HA} / S_{HA}$$

Descriptive term	Part of solvent required for 1 part of solute
Very soluble	Less than 1

Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Table No. 23: Relative terms of solubility

Medium Used	Solubility in mg /ml
0.1N HCl	455.86
D.M. water	583.76
4.5 pH acetate buffer	569.50
5.5 pH acetate buffer	569.361
6.8 pH phosphate buffer	574.76

Table No. 24: Effect of pH on solubility of the pseudoephedrine HCl drug

For a weak base, the following equation can be derived:

$$ST = SB + [H3O+] SB / Ka$$

Which indicates that solubility of weak base increases with decreasing ph (increasing H3O+ concentration) so as the ↓ ph then the ↓B, ↑BH+, and ↑ST?

Correlation with Henderson Hasselbach: Maximum aqueous solubility for weak bases is attained at pH-pKa » -2, where 99% is in the ionized (BH+) form. Minimum solubility is at pH-pKa » 2 where 99% is in the unionized (B) form.

The logarithmic form can be used to predict the pH (pHp) above which the weak base would precipitate from solution:

$$pHp = pKa + \log S_B / S_T - S_B$$

Solubility of weak acids and weak bases in buffers vs. water:

• The solubilities of a weak acid and its conjugate base are identical in a buffer solution. The pH of the buffer solution determines the B/A ratio and the solubility will be the same for either form (weak acid or conjugate base). The same is true for a weak base and its conjugate acid.

• The solubilities of a weak acid and its conjugate base are different in water. Addition of the weak acid makes the water acidic so there is more of the unionized weak acid form present and solubility is low. Addition of the conjugate base makes the water basic so there is more of the ionized form present and solubility is high.

• The solubilities of a weak base and its conjugate acid are also different in water for a similar reason. Addition of the weak base makes the water basic so there is more of the unionized weak base form present and solubility is low. Addition of the conjugate acid makes the water acidic so there is more of the ionized form present and solubility is high.

Used Medium	Solubility(mg /ml)
0.1N HCl	35.66
D.M. water	0.6
4.5 ph acetate buffer	4.44
5.5 pH acetate buffer	0
6.8 pH phosphate buffer	0

Table No. 25: Effect of pH on the solubility of loratadine drug

(2) Drug excipient compatibility (Stability in presence of excipient)

A drug or active principle is most often delivered to patient along with other chemical substance within a pharmaceutical formulation, which should comply with strict specification, often prescribed by law. In order to be approved a formulation should warrant well defined level of stability safely and efficacy. The desired level of stability is often difficult to achieve because the active principle may interact with the other substances of the formulation, the so called excipient which do not have a specific pharmaceutical activity.Owning to the length and complexity of the approval process, it is of paramount importance to address the drug-

Excipient. Compatibility issue from the early stage of Preformulation. The standard "Fast stability test" involves storing binary drug-Excipient mixture under extreme temperature and humidity condition and periodically determining the drug concentration Possible pitfall of this test is that concentration dependent effect are usually not identified, while some of the reaction observed at high temperature / humidity may not occur in normal stage storage.

Need of drug excipient compatibility study

1.) To provide the information to the formulator this will help to select the excipient for formulation of dosage form

2) To check whether the stability is ascertain during the toxicological study during the toxicological study.

3) To check the shelf life of drug in presence of excipients.

4) To check the loss of pharmaceutical elegance (fading of colored solution and tablets).

5) To check the bioavailability in presence of different excipients.

6) To check the loss of active ingredient.

In this study the excipients were selected which are generally used in tablets formulation Ratio of drug vs. excipient is taken as per their concentration in prototype development formula. To maximize possible physico-chemical interaction, drug and excipients were mixed together into two ways as follow

(1) Drug was mixed with excipient in Dry Form kept in a colorless and transparent vial with rubber plug and aluminum seal.

(2) Drug was mixed with excipient in dry form then granulated with water and IPA then dried these dried granules are kept in colorless and transparent vial with rubber plug and aluminum seal. All the samples as described below were kept at 25°C, 25 °C / 60% RH,40° C, 40° C/75% RH

Incubation Conditions: 40° C/75% RH

Intervals: 7 days, 15 days, 30 days

Quantity: Approx 100 mg/ vial

Packing Material: USP Type-I clear and transparent glass vials of capacity 10 ml, grey butyl rubber plugs and Aluminum seals

S.No.	Name of Excipient	Drug: Excipient ratio	Initial color	After 7 days	After 15 days	After 30 days
1.	Corn Starch	1:1	White fine powder	No change	No change	No change
2.	LactoseMonohydrate	1:1	White fine powder	No change	No change	No change
3.	Microcrystalline Cellulose ranq	1:1	White free flowing granular powder	No change	No change	No change
5.	Polyvinyl Pyrrolidone (Povidone K-30)	4:1	Light yellowish-white fine powder	No change	No change	No change
6.	Sodium Starch Glycolate (Primogel)	4:1	White fine powder	No change	No change.	No change
7.	Colloidal Silicon Dioxide (Aerosil-200)	10:1	White fluffy free flowing powder	No change	No change	No change
8.	Magnesium Stearate	10:1	White fine powder	No change	No change	No change

9.	Talc	5:1	White color fine powder	No change	No change	No change
10	Sunset yellow Lake	10:1	Colored fine powder	No change	No change	No change

Table 26: Compatibility study of loratadine with excipients to determine change in Color.

S. No.	Name of Excipient	Drug: Excipient ratio	Initial color	After 7 days	After 15 days	After 30 days
1.	HPMC K100M	1:1	White color	No change	No change	No change
2.	Ethyl cellulose	1:1	White color	No change	No change	No change
3.	Dicalcium phosphate dehydrate	1:1	White color free flowing	No change	No change	No change
4.	Polyvinylpyrollidone	4:1	White color fine	No change	No change	No change
5.	Talc	5:1	White color fine	No change	No change	No change
6.	Colloidal SiO_2	10:1	White fluffy free flowing powder	No change	No change	No change
7.	Magnesium stearate	10:1	White fine powder	No change	No change	No change

Table No.27: Compatibility study of pseudoephedrine hydrochloride with excipients to determine change in color

8.3 Standard curve of psrudoephedrine HCl in D.M water:

Psrudoephedrine HCl (100 mg) was accurately weighed and dissolved in 100 ml D.M water. Then 10 ml of this solution was transferred to another 100 ml volumetric flask to obtain a stock solution of 100 µg/ml. Different dilutions were prepared as per the Table. The absorbance were taken on double beam UV spectrophotometer using λ_{max} 257nm.The results are submit in Table 11 as Fig.8 . Similarly, this standard curve were prepared in 0.1N HCl, acetate buffer pH 7.4, acetate buffer pH 5.5,phosphate buffer pH 6.8.

S.No.	Vol.of Stock (ml)	Final Vol. (ml)	Concentration (µg/ml)	Absorbance λ_{max} (257 nm)
1.	0	100	0	0
2.	2	100	2	0.052
3.	5	100	5	0.134
4.	10	100	10	0.221
5.	15	100	15	0.345
6.	20	100	20	0.531
7.	25	100	25	0.612
8	30	100	30	0.770

Table No.28: Standard curve values of psrudoephedrine HCl

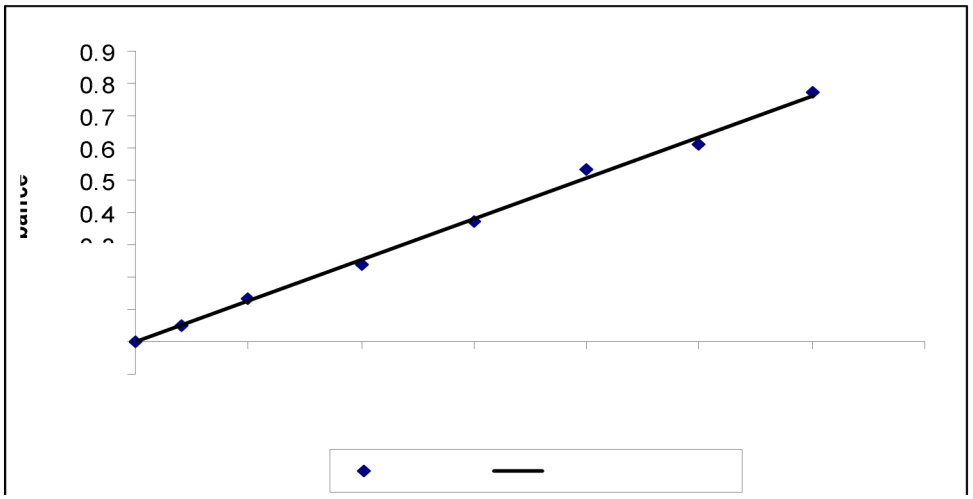


Figure No. 9

8.4 Standard curve of loratadine in 0.1 NHCl:

Loratadine (100 mg) was accurately weighed and dissolved in 100 ml of 0.1 N HCl solution. Then 10 ml of this solution was transferred to another 100 ml volumetric flask to obtain a stock solution of 100 µg/ml. Different dilutions were prepared as per the Table. The absorbance were taken on double beam UV spectrophotometer using λ_{max} 280nm.The results are submit in Table 12 as Fig.9.Similarly, this standard curve were prepared in 0.1N HCl, acetate buffer pH 7.4, acetate buffer pH 5.5,phosphate buffer pH 6.8.

S.No.	Vol.of Stock (ml)	Final Vol. (ml)	Concentration (µg/ml)	Absorbance λ_{max} (280 nm)
1.	0	100	0	0
2.	2	100	2	0.061
3.	5	100	5	0.114
4.	10	100	10	0.227
5.	15	100	15	0.350
6.	20 100	20	0.467	
7.	25	100	25	0.571
8	30	100	30	0.672

Table No.27: Standard curve values of loratadine in 0.1 N HCl

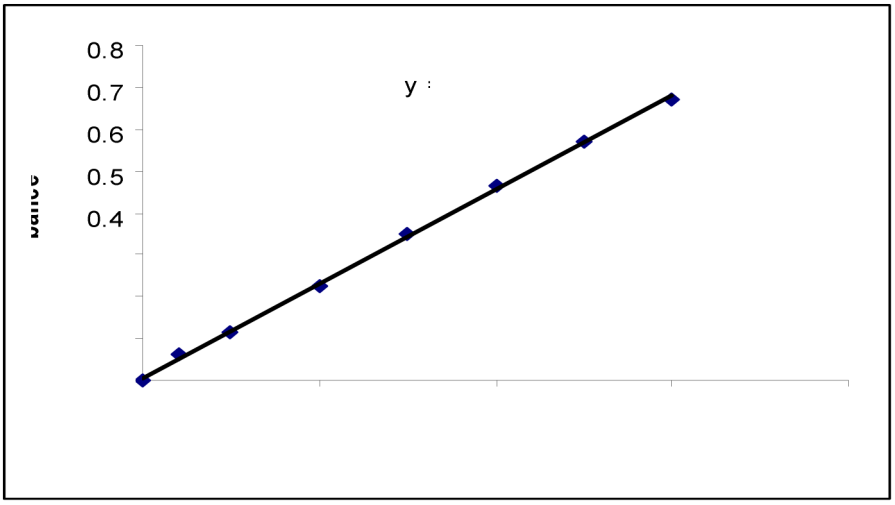


Figure No. 10

8.5 Analysis of innovator product

A comparative analysis of innovator product and formulator product helps in calculation of the (f_1) dissimilarity & (f_2) similarity dissolution factor. Analysis of the innovator product was carried out for various physical parameters and *in-vitro* dissolution profile.

Parameters:

- Shape.
- Thickness test.
- Hardness test.
- Friability test.
- Weight Variation test.
- *In-vitro* dissolution studies.
- Drug content uniformity test.

S. No.	Physical appearance	Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	D.T. IR layer (seconds)	Assay %
1.	12.5mm diameter. Two layer one sunset yellow and one white	598-601	4.22±0.3	4-5	41-51	SR 98.23% IR 102.2%
2.		599-605.3	4.02±0.1	4-3		
3.		598-601.9	4.20±0.4	5-4		
4.		599-601.1	4.22±0.3	5-6		
5.		598-603.5	4.21±0.2	4-3		
6.		599-602.1	4.20±0.3	4-3		
	Average	602.4	4.15	4.33		

Table No.30: Analysis of innovator product data sheet

9. Experimental Work:

Materials:

S. No.	Excipient	Category
1	Loratadine	API
2	Corn Starch	Diluent
3	LactoseMonohydrate	Diluent and binder
4	Microcrystalline Cellulose (Avicel PH 102)	Diluent
5	Aerosil	Binder
6	Sodium lauryl sulfate	Wetting agent
7	Magnesium Stearate	Lubricant

8	Sunset yellow colour	Color
9	Talc	Glident

Table No.31: Materials for immediate release layer (Loratadine)

S. No.	Excipient	Category
1	Pseudoephedrine HCl	API
2	HPMC K100M	Hydrophilic polymer
3	Ethyl cellulose	Polymer ,binder
4	Dicalcium phosphate dihydrate	Diluent
5	Colloidal Silicon Dioxide (Aerosil-200)	Glidant
6	Polyvinylpyrollidone [PVP K30])	Binder
7	Talc	Glidant
8	Isopropyl alcohol IP	Vehicle
9	Magnesium stearate	Lubricant

Table No. 32: Materials for sustained release (Pseudoephedrine HCl layer)

Formulation development

S. No.	Trials				
	Method of Formulation	**Wet Granulation**	**Wet Granulation**	**Wet Granulation**	**Wet Granulation**
	Ingredients	P1	P2	P3	P4
1	Pseusdoephedrine HCl	120	120	120	120
2	Talc	5	5	5	5
3	Magnesium stearate	2	2	2	2
4	Colloidal silica	3	3	3	3
5	Starch	20	-	-	
6	PVPK 30	-	20	20	20
7	Purified Water	q.s	q.s	-	q.s
8	Isopropyl alcohol	-		q.s	q.s
9	HPMC K100M	160	160	160	160
10	Ethyl cellulose	40	40	40	40
11	DCP Anhydrous	50	50	50	50

S. No.	Trials				
	Method of Formulation	**Direct compression**	**Slugging**	**Slugging**	**Slugging**
	Ingredients	P5	P6	P7	P8
1	Pseusdoephedrine HCl	120	120	120	120
2	HPMC K100M	160	160	160	160
3	Ethyl cellulose	40	40	40	40
4	Colloidal silica	3	2	2	2
5	Talc	5	5	5	5
6	Magnesium stearate	2	2	2	2
7	PVPK-30	20	20	20	20
8	Lactose anhydrous	-	50	35	25
9	DCP anhydrous	-	-	15	25
10	Magnesium stearate	-	2	2	2

S.No	Trials					
	Method of Formulation	**Slugging**	**Slugging**	**Slugging**	**Slugging**	**Slugging**
	Ingredients	P9	P10	P11	P12	P13
1	Pseusdoephedrine HCl	120	120	120	120	120
2	HPMC K100M	4	4	4	4	4
3	Ethyl cellulose	2	2	2	2	2
4	Colloidal silica	2	2	2	2	2
5	Talc	5	5	5	5	5
6	Magnesium stearate	2	2	2	2	2
7	PVPK-30	20	20	20	20	20
8	Lactose anhydrous	-	45	15	25	-
9	DCP anhydrous	50				-
10	DCP dihydrate	-	5	35	25	50
11	Magnesium stearate	2	2	2	2	2

S. No.	Trials				
	Method of Formulation	**Wet Granulation**	**Wet Granulation**	**Wet Granulation**	**Wet Granulation**
	Ingredients	**L1**	**L2**	**L3**	**L4**
1	Loratadine	5	5	5	5
2	Lactose Monohydrate	80	80	80	83.3
3	Maize Starch	-	28	25	31.23
4	Color sunset yellow Lake	0.50	0.50	0.50	0.53
5	Sodium lauryl sulfate	-	-	3	-
6	Maize Starch (P)	38	10	10	5
7	Purified Water	q.s	q.s	q.s	q.s
8	Microcrystalline Ranq 102	50	50	50	50
9	Color sunset yellow Lake	0.50	0.50	0.50	0.540
10	Maize Starch (Dried)	22	22	22	20
11	Aerosil	2	2	2	2
12	Magnesium stearate	2	2	2	2.3

Manufacturing process:

Wet granulation process steps (Loratadine)

1. All excipient was weighed according to formula and passed drug and excipient by #40 sieve except magnesium stearate and color sunset yellow.
2. Drug and lactose was mixed dried starch and color (#60 sieve passed) and dry mixing is done manually in polybag.
3. Slurry was made of starch using water as vehicle (starch: vehicle:: 1:4) and heated till translucent paste was formed.
4. Granules was made with help of granulator and dry at 70° C in FBD for till semidry mass obtained then passed form #16 mesh sieve and then again dry till LOD reaches at 3 to 4 % and final granules was obtained by passing it #24 sieve.
5. Granules were mixed with extra granular portion and color (#60sieve passed) for 20 min.
6. Aerosil -200 and talcum were passed #40 sieve and mixed for 5 min.
7. Magnesium stearate was passed form #60 sieve and mixed for 1 min.

Direct compression process steps[37] (pseudoephedrine HCl):

1. All excipient was weighed according to formula and passed drug and excipient by #40 sieve except magnesium stearate.
2. Drug and polymers was mixed thoroughly for 10 min. and prepared homogenous mixture manually in polybag.
3. Other excipient was added and mixed for 20 min.
4. Aerosil -200 and talcum was passed through #40 sieve and mixed for 5 min.
5. Magnesium stearate was passed from #60 sieve and mixed for 1 min.

Dry granulation process steps (pseudoephedrine HCl):

1. All excipient was weighed according to formula and passed drug and excipient by #40 sieve except magnesium stearate.

2. Drug and polymers was mixed thoroughly for 10 min. and prepared homogenous mixture manually in polybag.
3. Other excipients was added and mixed it for 20 min.
4. Magnesium stearate was passed from #60 mesh sieve and mixed for 1 min.
5. Compressed blend using 16mm FB punch and at weight range between 1000 to 1400 mg and hardness between 3-4 kg/cm^3
6. Tablets passed through multimill to form granules and then passed through #16 sieve and final passed #24 sieve.
7. Extra granular portion was added and mixed for 20 min.
8. Aerosil -200 and talcum was passed through #40 sieve and mixed for 5 min.
9. Passed magnesium stearate from #60 mesh sieve and mixed for 1 min.

Compression steps:

1) First compressed pseudoephdrine HCl layer and weight was adjusted 400mg.
2) Loratadine layer was compressed and weight was adjusted 200 mg.
3) Pseudoephedrine HCl layer was placed on loratadine one by one and then compressed both layer

Trials No.	Loss on drying (%w/w)		Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hauser's ratio	Angle of repose (fixed funnel method)
	I*	II**					
1	2.56	2.45	0.508	0.564	9.92	1.11	N.A
2	2.81	2.61	0.523	0.585	10.59	1.11	N.A
3	3.72	3.55	0.524	0.585	10.42	1.11	N.A
4	4.02	3.73	0.512	0.549	6.73	1.07	N.A
5	3.26		0.556	0.643	13.53	1.15	35.25 ^{o}
6	3.02		0.556	0.697	20.23	1.25	32.5 ^{o}
7	3.89		0.556	0.663	16.13	1.19	37.4^o
8	2.89		0.559	0.682	18.03	1.22	36.7^o
9	4.50		0.587	0.693	15.29	1.18	34.46^o
10	4.56		0.573	0.687	16.59	1.19	35.73^o
11	4.05		0.563	0.695	18.97	1.23	35.75^o
12	4.25		0.578	0.687	23.56	1.18	35.35^o

13	3.98	0.550	0.684	19.59	1.24	34.25 °

Table No.37: Pre compression parameters of Pn trials

I* = after drying I=after Lubrication**

Trial No.	Loss on drying (%w/w)		Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hauser's ratio	Angle of repose (fixed funnel method)
	I*	II**					
L1	2.56	2.75	0.575	0.682	20.08	1.186	35.02o
L2	2.81	3.37	0.505	0.645	21.70	1.277	34.46o
L3	2.72	3.15	0.587	0.691	15.05	1.177	34.28o
L4	2.45	3.42	0.545	0.656	16.92	1.203	32.25o

Table No. 38: Pre compression parameters of Ln trials

I* = after drying I=after Lubrication**

9. Evaluation of formulation[38]:

9.1 Physical evaluation:

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated .The weight variation values are tabulated in the table.

Hardness of tablets:

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 4-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation

was determined by Monsanto hardness tester. The hardness and standard deviation values are tabulated in table.

Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 10 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 100 ratation. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

% friability = [(W1-W2)100]/W1

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

The friability values are tabulated in table

Trails	Average Wt (mg)	Thickness (mm) (Mean ± S.D.)*	Hardness (kg/cm^2)	Friability
P1+L2	568-630	4.01±0.1	5-6	0.21
P2+L3	575-620	4.02±0.2	4-6	0.45
P3+L4	597-612	4.01±0.4	2-3	0.78
P4+L4	578-609	4.04±0.3	4-5	0.41
P5 +L4	594-609	4.02±0.2	5-6	0.12
P6 +L4	603-6016	4.01±0.3	2-3	0.65
P7 +L4	598-619	4.02±0.1	4-5	0.73
P8 +L4	586-617	3.98±0.2	2-3	0.63
P9 +L4	596-612	4.04±.03	3-4	0.53
P10 +L4	592-618	4.0±0.3	4-5	0.59
P11 +L4	594-619	4.02±0.2	2-3	0.33
P12 +L4	603-609	4.0±0.3	4-5	0.38
P13 +L4	595-608	4.0±0.2	4-5	0.36

Table No. 39:Post compression parameters of all trials

***n=3 Note wt variation present in P1, P2, P4**

9.2 Assay:

The chromatographic conditions described was used.

- System :Waters 2695
- Column : A stainless steel column 250 x4.6 mm,5µm C_{18}(250 cm X 4.6 mm, 5 microns) or equivalent
- Flow rate: 1.5 ml/min,
- Mobile Phase: Acetonitrile:Water:Tri ethyl amine : :600ml:400ml:1ml

  Final adjust pH3.5 by orthophosphoric acid
- Wavelength: 254 nm,
- Injection volume: 20 µl,
- Run time: 1.5ml/min,
- Column temperature: 35°C.

Standard preparation: Standard of pseudoephedrine hydrochloride 240mg & loratadine 10mg was taken in 50ml volumetric flask. 25ml diluents was added and mixed. Volume was adjusted with 50 ml of mobile phase and directly injected.

Test preparation: 20 tablets was weight and average weight was determined and the tablets were crushed to powder. Equivalent weight to pseudoephedrine hydrochloride 240mg & Loratadine 10 mg (two tablets) was taken in 50 ml volumetric flask. 25ml diluents was added sonicated for 15 minutes. Volume was made up with 50ml mobile phase and filtered. Filtered solution was injected directly.

Procedure: Assay was carried out in HPLC (waters system) including pump, photodiode array detector .separately inject 20 µl of the Standard and the Sample Preparation in to the liquid chromatograph and record the area for the major peak.

Calculation:

$$\% \text{ of Drug} = \frac{A_T}{A_S} \times \frac{W_1}{100} \times \frac{100}{W_2} \times \frac{P}{100} \times \text{Average weight}$$

A_T= Average of the area count of the Drug peak obtained from the chromatograms of the test aliquots.

A_S =Average of the area count of the Drug peak obtained from the chromatograms of the standard aliquots.

W_1 = Weight of the working standard taken in mg.

W_2 = Weight of the working Test taken in mg

` P=Potency of standard

Avg .Weight=Average weight in mg

Trials	Drug content (in %)** (Mean ± S.D.)	Trials	Drug content (in %)** (Mean ± S.D.)
P5	101.53 ± 7.89	L1	98.26±2.56
P6	98.58 ± 0.99	L2	99.45±1.12
P7	97.22 ± 1.78	L3	103.54±0.12
P8	99.29 ± 1.07	L4	97.25±0.45
P9	99.24 ± 2.68		
P10	96.24 ± 0.81		
P11	97.90 ± 1.92		

P12	101.18 ± 1.84		
P13	100.54 ± 1.35		

**n=3

Table No. 40: Drug content uniformity

9.3 Dissolution

for pseudoephedrine HCl B.P

Apparatus: USP II (paddle) dissolution test apparatus

Speed: 50rpm

Medium: Demineralized water

Volume: 900ml

Time: 2, 4, 6,8and 10 hrs

Temperature: $37^0 \pm 0.5^0C$

λ_{max}: 257nm

Standard: 65.0mg pseudoephedrine HCl B.P was taken in 50ml volumetric flask shacked vigorously up to dissolved with help of sonicator and Up to 50ml volume was made up with demineralized water.

5ml was taken from above solution and 50ml volume was made up with demineralized water.

Calculation:

Factor: - $\frac{1}{A_s} \times \frac{W_1}{100} \times \frac{5}{5} \times \frac{500}{L.C} \times \frac{P_1}{100} \times 100$

W_1 = weight of working Standard

L.C= Label claim in mg

P_1 = % potency of working Standard

A_s= Absorbance of standard

For loratadine USP:

Apparatus: USP II (paddle) dissolution test apparatus

Speed: 50rpm

Medium: 0.1M Hydrochloric Acid

Volume: 500ml

Time: 30, 45 min.

Temperature: $37^0 \pm 0.5^0$C

λ_{max}: 280nm

Standard: 20.0mg loratadine was taken in 100ml volumetric and vigorously shacked up to dissolved with help of sonicator. Then volume was made up to 100ml with 0.1M hydrochloric acid. 5 ml was taken from above solution and volume was made up to 100ml with 0.1M hydrochloric acid.

Procedure: 6 tablets was taken and each one transfered to a vessel containing 500ml of 0.1M HCl. Apparatus was switched on and care taken to ensure no air bubble of the surface of the tablets. After 30 minuets 10ml of sample was pipette out from each vessel at time 30 and 45 minuets and filtered. The filtrated taken and absorbance was noted.

Calculation

Factor: - $\frac{1}{A_S} \times \frac{W_1}{100} \times \frac{5}{5} \times \frac{500}{L.C} \times \frac{P_1}{100} \times 100$

W_1 = weight of working Standard

L.C= Label claim in mg

P_1 = % potency of working Standard

A_s= Absorbance of standard

Time (min)	Formulation				
	Innovator	**L1**	**L2**	**L3**	**L4**
15	64.23	57.45	63.6	56.25	69.2
45	98.56	92.33	97.82	108.25	102.6

Table No. 41: Dissolution profile of IR in different trials (0.1N HCl)

9.3 Kinetics of release

Model dependent approach

In order to analyze the release mechanism, several release models were tested such as:

Higuchi

$$Q_t = K_H \sqrt{t}$$

Where *Q*t is the amount of drug released at time *t* and *K*H is the Higuchi release rate; this is the most widely used model to describe drug release from pharmaceutical matrices.

Zero Order :

$$Q_t = Q_0 + K_0 + t$$

Where *Q*t is the amount of drug released at time *t*, K_0 is the apparent dissolution rate constant or zero order release constant, and Q_0 is the initial concentration of the drug in the solution resulting from a burst effect; in this case the drug release runs at a constant rate.

First Order:

$$\text{In } Q_t = \text{In}Q_0 + K_1$$

Where *K*1 is the first order release constant; in this case the drug released at each time is proportional to the residual drug inside the dosage form.

Korsmeyer–Peppas:

$$Q_t/Q_\infty = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristics of the drug dosage form and *n* is the release exponent, indicative of the drug release mechanism.

Estimation of parameters using Korsemayer equation

$$\log Mt/M\alpha = \text{Log } k + n \log t$$

Where,

Mt /Mα = the fractional release of the drug

t = release time

k = a constant depending on the structural and geometric characteristics of the release device.

n = the time exponent indicative of the release mechanism

In order to compare the differences for the release profiles between the tablets and their halves a simple model independent approach using a difference factor (*f*1), a similarity factor (*f*2).

The cumulative amount of pseusdoephedrine HCl released from the formulations at different time intervals was fitted to zero order kinetics using least square method of analysis. The correlation coefficient between the time and cumulative amount released was calculated to find the fitness of the data to zero order kinetics. The data were also subjected to first order kinetics by determining the correlation coefficient between the time and the log percent of pseusdoephedrine HCl to be released from the formulation. The data were also subjected to Higuchi's model by plotting the cumulative percent pseudoephedrine released against square root of time. Fitness to Higuchi's model was assessed by determining the correlation coefficient between the square root of time and the cumulative amount of pseusdoephedrine HC released from the formulations.

The cumulative percent of drug released from the formulations was plotted against time on log–log scale, and analyzed for linearity using Least-Squares Method. Calculating correlation coefficients between time and the cumulative percent of drug released on log–log scale tested the fitness of the data.

Release exponent	Release mechanism
0.5	Fickian diffusion
0.5< n <1	Non-fickian diffusion/Anomalous transport
1	Case-II transport/Zero order release
> 1	Super case II transport

Table No.42: Release exponent and release mechanism

Time (hrs)	Trials									
	Inno.	P 5	P 6	P 7	P 8	P9	P 10	P 11	P12	P13
2	31.81	55.96	58.75	54.24	50.23	45.26	56.26	48.45	45.24	42.28
4	55.5	77.28	68.36	66.13	62.45	55.92	73.92	64.23	56.13	50.63
6	64.23	95.88	80.65	88.65	79.08	63.63	89.23	79.6	74.23	70.56
8	77.96	99.27	90.75	95.11	88.28	78.76	97.42	89.26	89.62	85.66
10	86.96	99.65	98.05	97.16	92.67	89.72	99.23	96.76	100.28	92.73

Table No. 43: Zero order release profile

Cumulative percent drug dissolved Vs time (D.M. water)

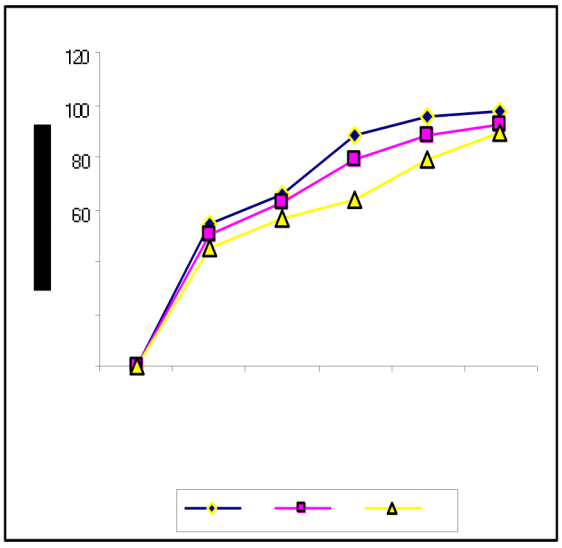


Figure No. 11.1

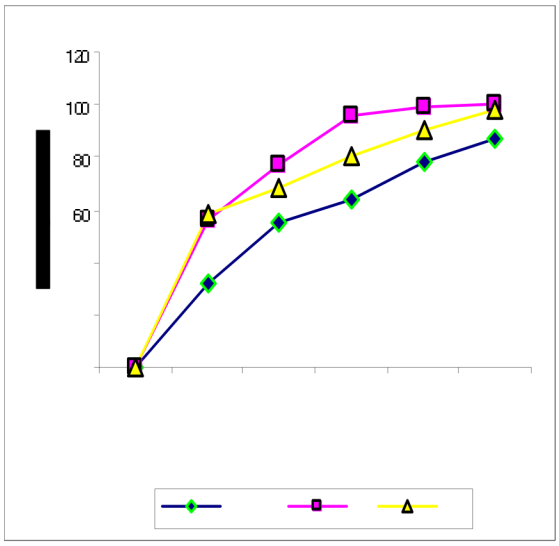


Figure No. 11.2

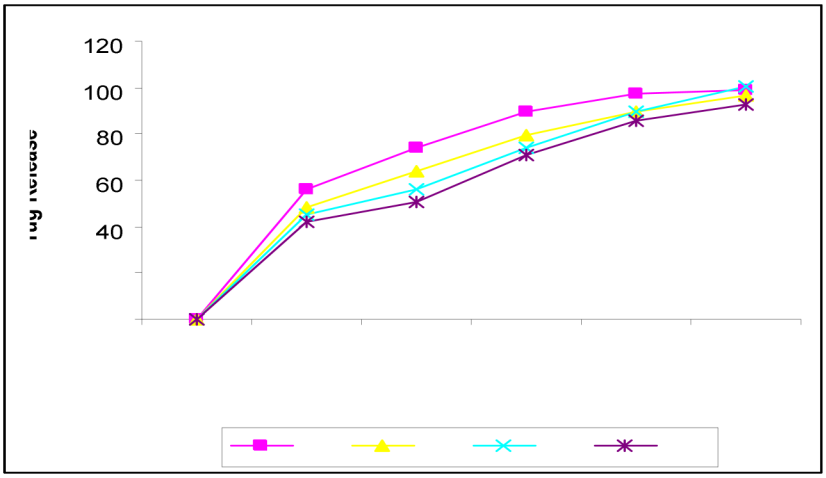


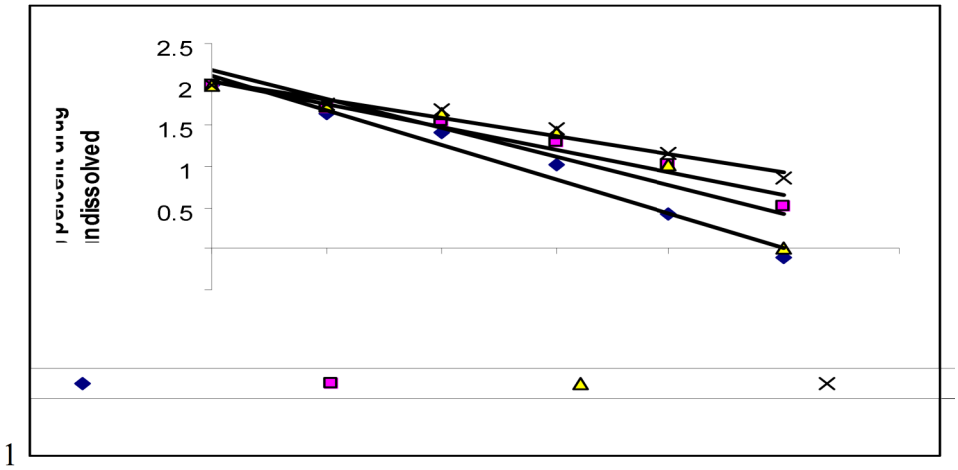
Figure No. 11.3

Table No.44: First order release profile

Log Percent Drug undissolved V/s Time

Time	Formulation									
	Inno.	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**
0	2	2	2	2	2	2	2	2	2	2
2	1.83	1.64	1.61	1.66	1.69	1.73	1.64	1.71	1.73	1.76
4	1.64	1.35	1.50	1.52	1.57	1.64	1.41	1.55	1.64	1.69
6	1.55	0.61	1.28	1.05	1.32	1.56	1.03	1.30	1.41	1.46
8	1.34	-0.13	0.96	0.68	1.06	1.32	0.41	1.03	1.01	1.15
10	1.11	-0.45	0.29	0.45	0.86	1.01	-0.11	0.51	-0.10	0.86

Figure no12.1



1

Figure no12.2

SRT*	Trials										
	Inno.	P 5	P 6	P 7	P 8	P9	P 10	P 11	P12	P12	P13
1.412	31.81	55.96	58.75	54.24	50.23	45.26	56.26	48.45	45.24	45.24	42.28
2	55.5	77.28	68.36	66.13	62.45	55.92	73.92	64.23	56.13	56.13	50.63
2.449	64.23	95.88	80.65	88.65	79.08	63.63	89.23	79.6	74.23	74.23	70.56
2.828	77.96	99.27	90.75	95.11	88.28	78.76	97.42	89.26	89.62	89.62	85.66
3.162	86.96	99.65	98.05	97.16	92.67	89.72	99.23	96.76	100.28	100.28	92.73

Table No. 45:Higuchi release profile

SRT*= Square root of time

Cumulative percent drug dissolved Square root of time:

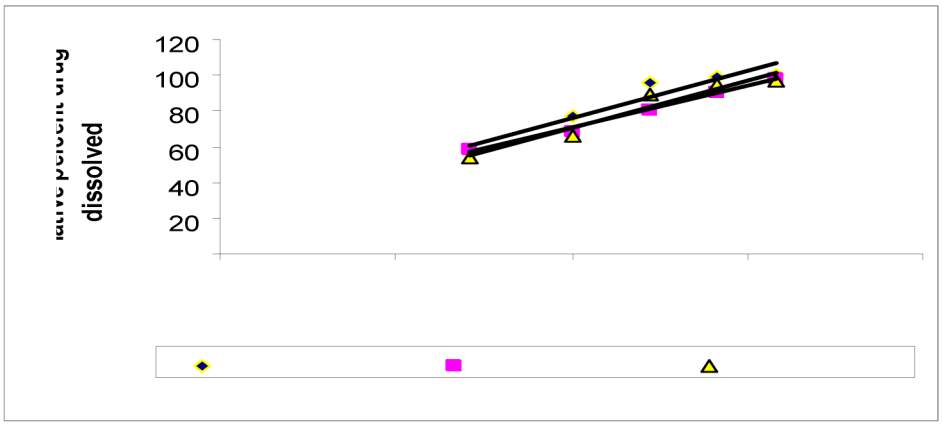


Figure No. 13.1

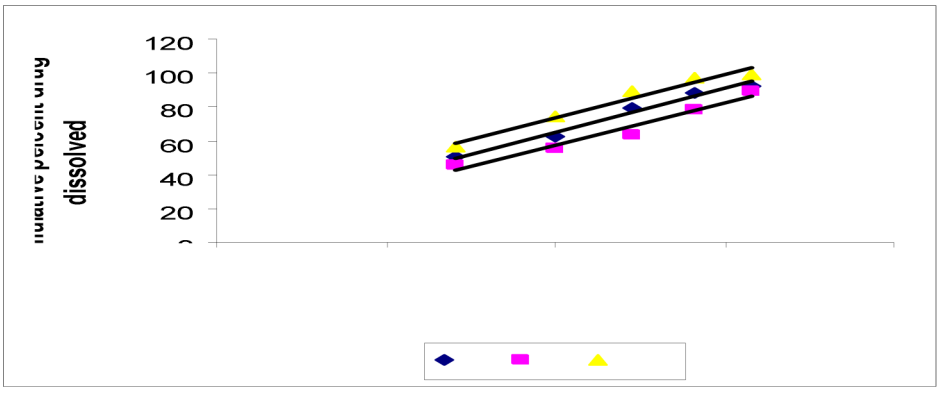


Figure No. 13.2

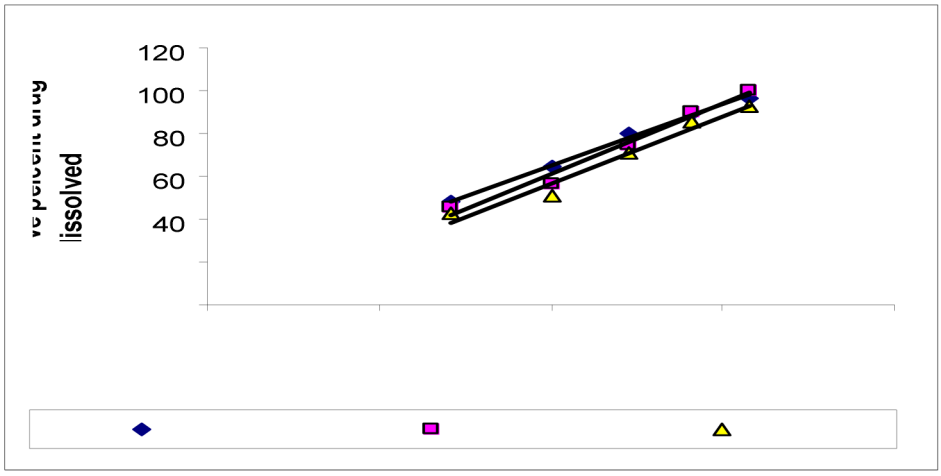


Figure No. 13.3

Log time	Log fraction drug released									
	Inno.	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**
0.301	-0.497	-0.252	-0.230	-0.265	-0.299	-0.344	-0.249	-0.314	-0.344	-0.373
0.602	-0.255	-0.111	-0.165	-0.179	-0.204	-0.252	-0.131	-0.192	-0.250	-0.295
0.778	-0.192	-0.018	-0.093	-0.052	-0.101	-0.196	-0.049	-0.099	-0.129	-0.151
0.903	-0.108	-0.003	-0.042	-0.021	-0.054	-0.103	-0.011	-0.049	-0.047	-0.067
1	-0.060	-0.001	-0.008	-0.012	-0.033	-0.047	-0.003	-0.014	0.001	-0.032

Table No.46:Korsemayer plot

Log fraction drug released and Log time

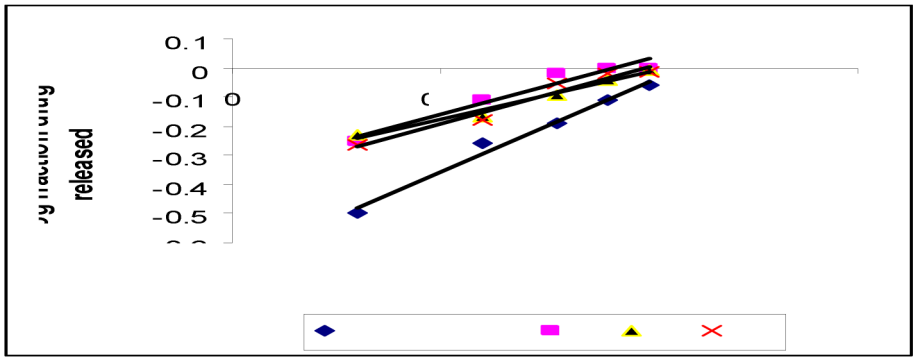


Figure No. 14.1

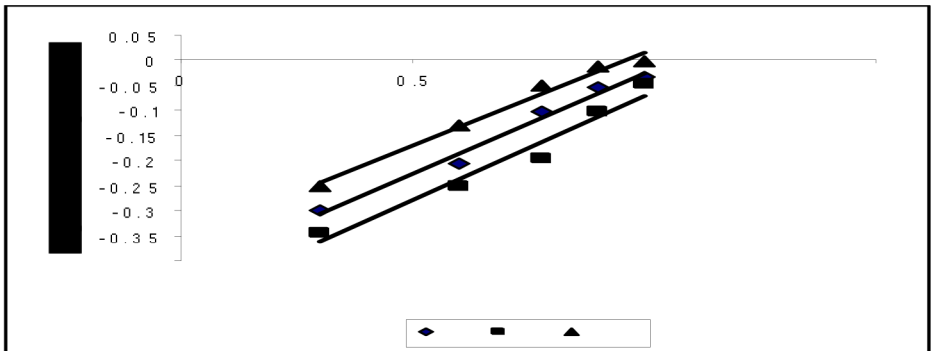


Figure No. 14.2

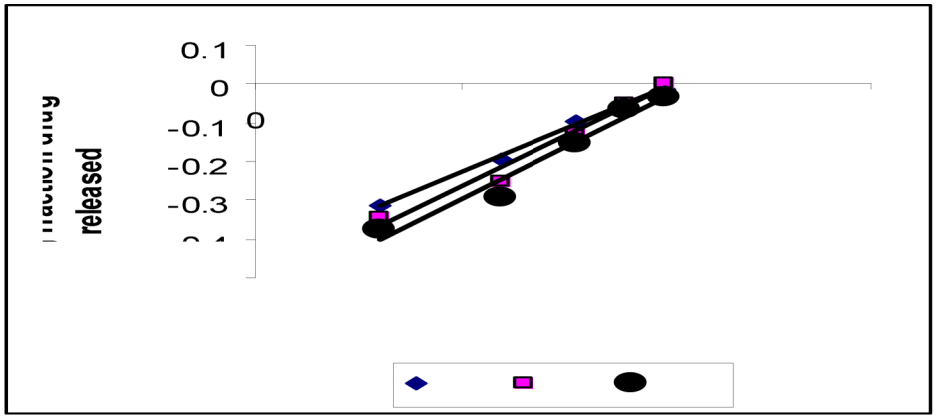


Figure No.14.3

Formulation	Zero order	First order	Higuchi	n value
Inno	0.981	0.994	0.994	0.614
P5	0.950	0.977	0.950	0.379
P6	0.933	0.953	0.933	0.511
P7	0.993	0.958	0.972	0.394
P8	0.993	0.996	0.993	0.400
P9	0.962	0.980	0.962	0.418
P10	0.934	0.987	0.934	0.370
P11	0.990	0.992	0.934	0.438
P12	0.988	0.988	0.990	0.510
P13	0.997	0.999	0.988	0.519

Table No.47: In vitro dissolution kinetics of matrix tablets

9.4 Comparison of dissolution profile:

9.4.1 Purpose of dissolution profile comparison:

- In order to compare the differences in the release profile between the references to test simple model independent approach using a difference factor (f1) and similarity factor has been adopted by FDA.
- For accepting product sameness under SUPAC-related changes.
- To waive bioequivalence requirements for lower strengths of a dosage form.
- To support waivers for other bioequivalence requirements.

9.4.2 Model Independent Approach Using a Similarity Factor

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles. The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |] / [\Sigma_{t=1}^{n} R_t]\} \cdot 100$$

where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent(%)dissolution between the two curves

$$f_2 = 50 \bullet \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n} [\bar{R}(t) - \bar{T}(t)]^2}{n}}} \right]$$

A specific procedure to determine difference and similarity factors is as follows:

1. Determine the dissolution profile of two products of the test and reference products.
2. Using the *mean dissolution values* from both curves at each time interval, calculate the difference factor (f_1) and similarity factor ($f_{2)}$ using the above equations.
3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. As further suggestions for the general approach, the following recommendations should also be considered:

1. The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both the profiles should be

the same (e.g., 15, 30, 45, 60 minutes). The reference batch used should be the most recently manufactured product.

2. Only one measurement should be considered after 85% dissolution of both the products.
3. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.

4. The mean dissolution values for R_t can be derived either from (1) last t (reference) batch or (2) last two or more consecutively manufactured batches.

Formulation	F2 value
P5	32.01
P6	38.42
P7	37.26
P8	45.56
P9	60.24
P10	34.43
P11	44.65
P12	48.03
P13	56.65

Table No. 48: Similarity factor

Formulation	F1 value
P5	34.93
P6	25.31
P7	26.80
P8	17.77
P9	5.318
P10	31.47
P11	19.54
P12	15.49
P13	8.02

Table No.49: Difference factor

10. Stability studies of optimized formulation

The stability study was carried out by keeping them at 40ºC/75% RH for 3 month to assess their stability with respect to their physical appearance and release characteristics. The physical characteristics like weight variation, hardness, friability, disintegration time, and in vitro release profile were determined at interval of 15, 30, 45 and 60 days by packaging the tablets in sealed aluminum foil and kept in humidity chamber.

Formulation	Stability study period (Days)	Weight variation	Hardness	Friability	Drug content Pn	Drug content L4
L4+P9	0	596-612	4-5	0.23	96±0.39	
	15	595-615	6-7	0.51	96.2 ±0.56	
	30	589-615	6-7	0.52	95.8±0.31	
	45	598-609	5-6	0.50	97.2±0.33	
	60	588-618	2-3	0.79	96.2 ±0.56	
L4+P13	0	595-608	6-7	0.49	97±0.23	
	15	598-609	4-5	0.49	97.2±0.26	
	30	595-615	4-5	0.42	96.8±0.65	
	45	596-612	2-3	0.43	98.2±0.21	
	60	589-615	2-3	0.72	95. ±0.26	95.36

Table No. 50: Evaluation of tablets during stability study period (40ºC/75%RH)

Time (Hrs)	0 day	15days	30 days	45 days	60 days
2	42.28	44.24	45.2	47.96	46.03
4	50.63	60.65	55.15	65.25	60.56
6	70.56	69.23	66.5	78.15	71.13
8	85.66	79.35	77.5	85.5	80.3
10	92.73	94.25	92.5	95.5	92.95

Table No.51:Zero order release profile of P13 at 0, 15, 30, 45 and 60 days during the stability period

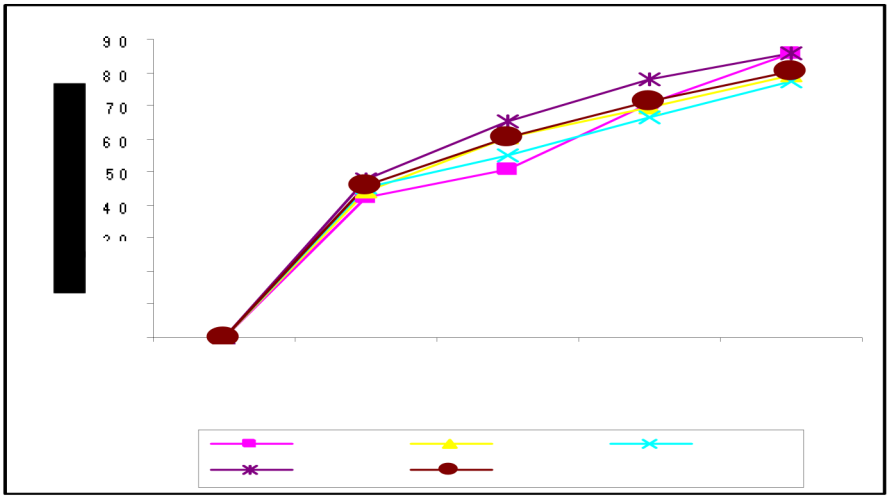


Figure No. 15

Time (Hrs)	0 day	15days	30 days	45 days	60 days
2	45.26	46.24	45.2	44.96	46.23
4	55.92	58.65	55.15	56.25	59.56
6	63.63	69.23	66.5	65.15	65.13
8	78.76	79.35	77.5	77.5	78.3
10	89.72	90.25	92.5	91.5	92.95

Table No. 52:Zero order release profile of P9 at 0, 15, 30, 45 and 60 days during the stability period

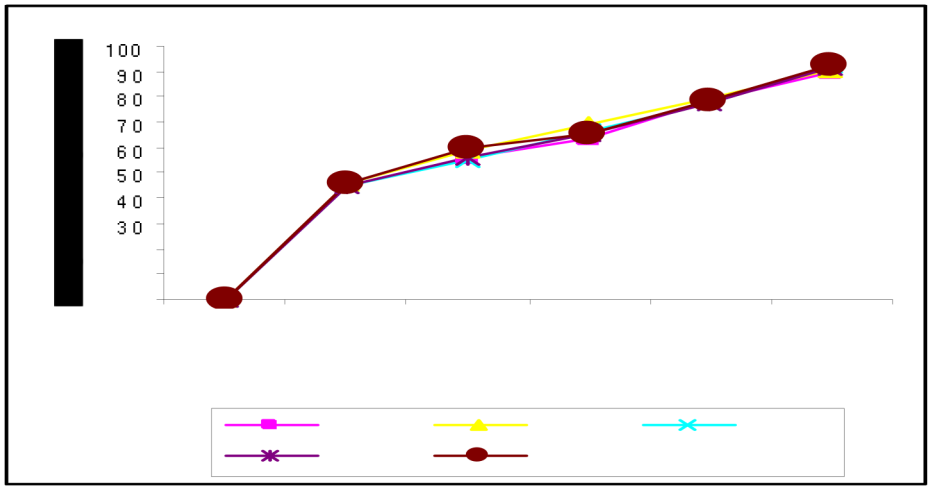


Figure No. 16

11. Results and discussion

In the present investigation sustained release matrix as well as immediate release bilayer tablets was prepared of two drug using hydrophilic polymer, HPMC K100M and different ingredient. The hydrophilic matrix tablets were prepared by different method wet granulation direct compression and slugging technique.

1. Preformulation Study:

1. API Characterization Study:

1.1 Angle of repose:

Pseudoephedrine HCl was 35.940 and it was passable as result shown in **table 14.**

Loratadine was cohesive in nature.

1.2 Bulk density and tapped density:

Tapped density was higher then bulk density and result are shown in **table 15** and respectively. Tapped density of pseudoephedrine HCl and loratadine was found 0.683 and 0.293 respectively.

1.3 Compressibilty index:

The flow characteristics of pseudoephedrine HCl was free flow and loratatdine was cohesive and drug stick with fennel result shown in **table no.15** and Hauusner's ratio result show in **table 17.**

1.3 pH dependent solubility Study:

pH of pseudoephedrine HCl and loratadine in 10% solution in methanol was found to 4.18 and 6.8 respectively. The pH dependent solubility study was carried out by using different pH buffer solution 0.1 N HCl ,D.M water , pH 4.5 acetate buffer, pH 5.5 acetate buffer and pH 6.8 phosphate buffer. Study showed solubility of loratadine was more in

pH 1.2 (0.1 N HCl) 35.66mg/ml and for pseusdoephedrine HCl 556.86 mg/ml as indicated in **table no.25 and 24** respectively.

1.3 Sieve Analysis of API:

The sieve analysis carried out by using mechanical shaker, showed that the average particle size of pseudoephedrine HCl was 250µm as given in **table no.20** for pseudoephedrine HCl. For loratadine micro analyzer is used and average particle size was 10 micrometers.

1.4. *Loss on Drying (LOD):*

As calculated, moisture content of pseudoephedrine HCl 0.42% and loratadine 0.37% respectively.

The flow properties of pure drugs were carried out and the results indicate that pseudoephedrine HCl has good flow and loratadine poor flow property and cohesive nature. In order to overcome this problem wet granulation technique was adopted using starch paste as binder to impart good flow as well as compressibility for loratadine because granules has good flow as compare to pure drug and for pseusdoephedrine HCl wet granulation ,direct compression and slugging used.

2. Compatibility Study:

Drug–Excipients compatibility study of pseudoephedrine HCl and loratadine with different categories of excipients was carried out. The study was carried out at accelerated conditions of temperature and humidity like 40°C/75%RH, and noted their physical appearance, and release profile after 15,30,45and 60 Days and compared with initial value and result shown in **table 26and 27.**

3. Evaluation of Formulation Parameters:

Evaluation was divided in mainly in to

- Pre compression parameters and
- Post compression parameters.

Pre compression parameters include loss on drying of dried granules and final blend, bulk density, tapped density, Carr's index, Houser's ratio and sieve analysis. In post compression parameters average weight, thickness, hardness, disintegration time and friability were determined.

3.1. Pre Compression Parameters:

- % LOD of dried granules maintained in that level 2 to3% by drying at 105°C and optimize drying time (5min.) shown in **tables no. 37 and 38**.
    - Bulk density in the range 0.508 – 0.593 gm/ml for Pn and 0.505 to 0.575 for Ln trails
    - Tapped density in the range 0.54-0.695 gm/ml for Pn and 0.641 to 0.594 for Ln trials
    - Carr's Index ranging

      P1 to P4 6.47 to9.92

      P5 20.23

      P6 to P13 11.56 to 15.29 to 23.56

      Ln trails 15.05 to 20.08
    - Hauser's ratio in the range 1.1-1.2 shows the good flow characteristics for both.
        - Wet granulation method was adapted in trials P1 to P4 trials and poor flow and color of granules was change during drying.
        - Direct compression method was adapted in trial P5 and sticking was observe, powder blend shows poor flow which causes weight variation and problem in content uniformity.
        - In P6 to P13 trials, granules was passable and pre compression.
        - In L1 to L4, it was found that granules have good flow property.L1 trials D.T was higher so we reduce binder concentration and molting also present so we change ratio in extra granular and intra granular.

3.2 Post compression parameter:

The tablets were evaluated for physical characteristics like weight variation, hardness, friability and drug content.

- The weight variation test was carried out for bilayer tablets and the values are shown in **table no. 39** respectively. The weight variation values of first four trials the tablets are in the range of 568 mg to 630 mg for bilayer tablets, which is more than 5% indicating that the variation in the weight of the tablets is out official limits but for remaining trails within range.
- The hardness test was carried out using Monsanto hardness tester. The hardness of the bilayer tablets are shown in **table no. 39** respectively. The tablet hardness was found to be uniform and in the range of approximate 4 to 5 kg/cm^2 which indicates that the prepared bilayer tablets are mechanically stable.
- The friability test was carried out by Roche friabilator. The percentage friability of bilayer tablets are shown in **table no. 39.** They are in the range of 0.21% to 0.73 % for bilayer tablets. They are less than the standard limit of 1% indicating that the prepared tablets are mechanically stable.

Drug content uniformity

The percent drug content values of bilayer tablets of each formulation are shown in **table no. 40** for both layer. They are in the range of 95% to 102% which is within standard limit of ± 5%. It indicates uniform distribution of drug in the tablets of each formulation.

In Vitro drug release studies:

- Drug release form P6 trial was at higher rate and trials P7, P8 intermediate
- P10 to P 12 release rate retard as concentration of DCP increase.
- P9 and P13 trials only contain only DCP as diluents so release was slowest as compared to other. **(Table No. 42)**

- The correlation coefficient values of zero order and first order release profiles of matrix tablets are 0.981 ,0.950 ,0.933, 0.972, 0.993 ,0.962 ,0.934 ,0.990, 0.988 ,0.99 and 0.994 , 0.97 ,0.953, 0.95, 0.996, 0.980, 0.987, 0.992 ,0.999 ,0.988 respectively**.(Table No. 47)**
- The correlation coefficient values of Higuchi plot are 0.994, 0.950, 0.933, 0.97, 0.993, 0.962, 0.934, 0.93, 0.990 and 0.988 for matrix tablets. **(Table No. 45)**
- P5, P6, P6, P8, P10, P11, P13 trials followed first order of kinetics.
- P7 trials follows zero order kinetics
- Only P13 trials follow Higuchi model
- Dissolution profile of loratadine was given in table no.39.

f_1 and f_2 Value:

Similarity factor (F_2) was calculated between innovator formulation and our formulation. Similarity factor value in the range of 50-100 indicates that there is similarity in the release profile of the formulations.

- In case of tablet formulation P5 to P13 shown f_1 value34.93 ,25.31, 26.80, 17.77, 5.318, 31.47 ,19.54 ,15.49 ,8.02 respectively, and f_2 value 32.01 ,37.26, 45.56, 60.24, 34.43, 44.65, 56.65 and 48.03 respectively.**(Table no.48 and 49)**
- The diffusional exponent values (n) for and P6,P7,P8 and P9 ranged from 0.32 to 0.41 indicating that the drug release from the matrix tablets followed fickian diffusion.
- The diffusional exponent values (n) for P10, P11, P12 and P13 ranged from 0.41 to 0.61 indicating that the drug release from the matrix tablets followed anomalous diffusion(non fickian).

Stability studies

The stability studies of the optimized matrix as well as bilayer formulation were done for about 2 months by sealing the tablets in aluminum foil and kept in humidity chamber.

- The physical characteristic like weight variation, hardness, friability, percent drug content during and in vitro release profile were determined at interval of 15, 30,45 and 60 days.

- The value of weight variation, hardness, friability and percent drug content during stability study for bilayer tablets are shown in the **table 50**. These values indicate that there was no significant change when compared with fresh samples.
- Dissolution study was carried out at each time interval for all the optimized formulation during the stability studies.
- The cumulative percentage drug released Vs time profile for matrix tablets are shown in **table 51 and 52**, and **figure 15 and 16** respectively. The results indicate that there is no significant change in the release profile of the formulations during the stability studies.
- The data obtained from the stability studies of the optimized formulation indicates that the tablets are stable

Selection of optimized formulation

f_1 and f_2 Value

In case of matrix tablets for the selection of optimized formulation the similarity factor and the difference factor are calculated between the marketed formulation and our prepared formulation. Similarity factor value in the range of 50-100 and difference factor value in the range of 0-15 indicates that there is similarity in the release profile of the two formulations.

- Formulation P9 showed the highest *f2* value of 60.24 and lowest *f1* value 5.318 and P13 showed the highest *f2* value of 56.65 and lowest *f1* value 8.02.

- The diffusional exponent values (n) for P13 was 0.61 indicating that the drug release from the matrix tablets followed anomalous diffusion(non fickian).

In Vitro drug release studies:

- The correlation coefficient values of Higuchi plot of P13 0.988 for matrix tablets. The correlation coefficient values are close to one which indicates that the drug release is by diffusion mechanism
- P13 trials only contain only DCP as diluents so release was slowest as compare to other because its insoluble in water.

Drug-excipients interaction studies

- The optimized formulations were subjected to FTIR studies to confirm whether or not there is drug polymer interaction.
- The results of the FTIR studies indicate that there was no interaction between the drug and polymers used in the formulation.

12. Conclusions

In the present study sustained release matrix as well as immediate release bilayer tablets was prepared using two hydrophilic polymers HPMC K100M and ethyl cellulose. From the results following conclusions can be drawn.

- The release of pseusdoephedrine HCl and loratadine from the bilayered tablets was analyzed by plotting the cumulative percent drug release v/s time. The initial high amount of loratadine release can be attributed to the release of drug from the immediate release layer of the formulations and the sustained release layer of pseudoephedrine HCl formulations exhibited prolonged drug release.

- Dissolution of loratadine was little affected by addition of SLS because the average particle size of drug was 10 µm

- The correlation coefficients of all the formulations for first order release kinetics were found higher when compared to those of zero order kinetic indicating that the drug released from all the formulations followed first order kinetics.

- Analysis of the dissolution profile on the basis of Higuchi's model suggested that the drug release was basically swelling and diffusion controlled.

- Data from the Korsemayer model suggested that drug release from formulations P12 andP13 was non-Fickian (anomalous) diffusion.

- While maintaining the HPMC K100M and drug level constant in the controlled release tablet formulations investigated, it was found that the type and level of excipients influenced the rate and extent of pseusdoephedrine HCl release.

- The percent average difference, based on f_2 values, between dissolution profiles of formulations containing soluble excipients compared to formulations containing insoluble excipients was in the range of 15–20%, indicating dissimilarities in the release profiles.

- The percent average difference between dissolution profiles of formulations containing a similar type of excipients (i.e., soluble or insoluble excipients) was in the range of 5–10%, indicating similarities in the profiles.

- The insoluble excipients, especially DCP, caused the drug to be released at a slower rate and to a lesser extent than the soluble excipients investigated. Formulations containing insoluble diluents (P9 and P13) were more similar to innovator product.

- Intermediate release profiles were obtained for pseudoephedrine HCl containing lactose and DCP were used in the formulation. The release mechanism of pseusdoephedrine HCl from each tablet formulation was described by Peppas's equation [non-Fickian (anomalous) diffusion].

- Different type diluents type and level used in the formulation did not have an impact on the release mechanism of pseusdoephedrine HCl from the tablets. The results of this study provide useful information on formulation optimization during development of controlled release tablet formulations.

- FT-IR studies revealed that there was no chemical interaction between the drug and the various polymers used in the study.

- Stability studies indicated that there was no significant change in the properties of matrix as well as bilayered tablets.

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